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INDEX

VOL 50 FASC 1

INDEX

VOL 50 FASC 2

(Cont from cover pag 2)

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INDEX

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50 YEARS

With publication of the present issue Acta Ophthalmologica commences its 50th volume which thus proclaims the Journal s existence throughout half a century

Acta Ophthalmologica appears as one of the many witnesses to profitable cooperation among the Scandinavian countries Denmark Finland Iceland Norway and Sweden with a total population of over 21 million The Scandinavian countries are linked with each other by strong geographical historical linguistic and cultural ties Periodic meetings of Scandinavian ophthalmologists have taken place since 1901 Our five Ophthalmological Societies are the owners of the Journal and approve its editorial policy

A jointly Scandinavian journal Nordisk Ophthalmologisk Tidsskrift was published during the years 1889–1892 and because it was written in our own languages it was inappropriate for dissemination to the rest of the world In contrast Acta Ophthalmologica s contents have always been published in English French or German

K K K Lundsgaard deserves mention for having taken the initiative in the negotiations which led to the publication of Acta Ophthalmologica in 1923 In recognition of his efforts his name appears on the front cover of the Journal

The periodical s first editors were from Denmark K K K Lundsgaard and Henning Ronne from Finland Emil Enroth and V Gronholm from Norway Sigurd Hagen and Ingolf Schiotz and from Sweden Fritz Ask and J W Nordenson The present Editorial Board includes all Professors from the Scandinavian university eye departments

In addition to original reports from the Scandinavian countries Acta Ophthalmologica also contains reports of the Scandinavian ophthalmological societies and the Scandinavian Congress of Ophthalmologists Approximately 15% of the articles originate from countries outside of Scandinavia

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From the Eye Department Oslo City Hospital Norway
(Head Prof dr med Jan Ytteborg)

ACUTE RETROBULBAR NEURITIS – A RETROSPECTIVE STUDY

BY

HANS OTTO SANDBERG

51 patients with the diagnosis of retrobulbar neuritis or papillitis have been re examined 3 to 7 years after presentation of their disease The patient population shows a dominance of females which is probably due to their greater motivation for hospitalization with minor symptoms We found an age distribution of patients exhibiting two maxima The maximum in the higher age group appeared to represent cases of retrobulbar neuritis or papillitis of vascular pathogenesis We found that vascular optic neuritis or papillitis did not carry as poor a prognosis for sight as previously reported in the literature In the older age group papillitis appears to be relatively more frequent than retrobulbar neuritis Acute retrobulbar neuritis or papillitis in the older age group seem to indicate a reduced life expectancy

Key words optic nerve – retrobulbar neuritis

Acute retrobulbar neuritis is defined as a condition affecting the optic nerve clinically recognized as a central scotoma of acute or subacute onset. The condition is often accompanied by pain aggravated by eye movements Pa

Received July 15 1971

The Journal is published bimonthly and the yearly number of pages is about 1000 In addition to this are the supplements which are usually Scandinavian doctoral dissertations and are automatically sent free of charge to subscribers Because of their monographic format they are especially useful In the last decade 47 supplements have been published

From its inception the Journal has had the same publisher – Munksgaard Through the years and especially after World War II Acta Ophthalmologica has continued its vigorous development and has emerged as an international journal with worldwide distribution with two thirds of the copies being sent to countries outside of Scandinavia

Having reached age 50 and flourishing Acta Ophthalmologica should give recognition to its roots in Scandinavian ophthalmological tradition and express its respect and appreciation of its founders whose activity resulted in its existence It is of course Acta Ophthalmologica's wish for the next 50 years not only to maintain its status but also to expand its position in the field of ophthalmology with continually increasing development communication and interaction

P Brændstrup

From the Eye Department Oslo City Hospital Norway
(Head Prof dr med Jan Ytteborg)

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Received July 13 19 1

pillitis is defined as a condition of the optic nerve having the additional features of hyperaemia and edema of the optic disc

The pathologic processsses underlying optic neuritis or papillitis are of diverse nature Demyelinating processes metabolic toxic vascular neo plastic or inflammatory lesions have all been identified as causes

This retrospective study was carried out to attempt to delineate the probable etiology from the clinical course of each patient

The patient material consisted of m patients from the Eye Dept at Ullevål Sykehus Oslo They were discharged from hospital with the diagnosis retro bulbar neuritis or papillitis during the 5 year period 1963–1967 Excluded from the study were those patients whose optical nerve affection was probably caused by tumor close to the optic chiasma temporal arteritis Leber s atrophy intoxi cation or specific inflammation The material thus comprised a selection of patients some of whom by inference suffered from demyelinating disease others who had no discernible cause for their condition

The first group consisted of patients presenting clinical signs and symp toms of multiple sclerosis The second group included patients with no signs or symptoms of this disease The material consisted of 63 patients of both sexes 7 patients have died 5 patients have changed place of residence and have not been traced Out of the original number 51 patients have been re examined

Table I
Etiology of the disease and sex distribution in the patient material

Etiology	Males	Females	Both
Unknown	15 *	24 **	39
Probable multiple sclerosis	4	9	13
Established multiple sclerosis	5	6	11
Total	24 (38 %)	39 (62 %)	63 (100 %)

* Includes a possible case of poisoning
** Includes a case of collagen disease and a case of Argyll Robertson pupil with negative WR in blood and CSF
The table includes the total material not merely the re examined patients

Females outnumbered males in this study by 39 to 24 (Table I) Similar observations occur in other studies (Fleischer 1908 Hyllested 1950 Hyllested & Møller 1961) Cibis s (1939) material contains more males than females but his material comprised many binocular lesions of the male group This was most evident in males of the 6th decade and possibly intoxications were re presented in that group There is no difference in incidence between the sexes in studies on multiple sclerosis Hyllested (1950) argues that the predominance of females presenting retrobulbar neuritis is perhaps due to an increased motivation for hospitalization with this sex Table II shows that a high pro portion of the females in the present study had lesser impairment of visual acuity at the time of admission to hospital than males which appears to sup port Hyllested s argument

The figure shows age incidence of patients with optic neuritic or papillitis of unknown etiology in contrast to those where multiple sclerosis was diagnosed or suspected The age incidence shows the same distribution pattern below 50 years of age for the two groups From this may be inferred that demyelinating neuritis may be included in the group of unknown etiology (Hyllested 1950) Furthermore it is apparent that age incidence in the group of unknown etiology reaches a new peak in the 7th decade The same pattern has been found by other investigators though the second maximum has been found at a somewhat lower age than in the present study (Cibis 1939 Collis 1965 Hyllested 1950

Table II

Visual acuity at time of admission to hospital

Visual acuity reduced to	6 6–6/8 5	6 9–6/18	6 20–6 60	6/60 or less
	No of eyes			
Males	[illegible]	3	8	14
Females	6	8	6	[illegible]
	Per cent			
Males	7 4	11 1	29 6	51 [illegible]
Females	15 0	0 0	15 0	50 0

The number of eyes exceeds patient number on account of binocular affections in several cases

Taub & Rucker 1954) 7 patients comprise the 7th decade group in the present material Only 2 are alive The other 5 have died either from cardiovascular causes or secondary to such causes as apparent from Table III It may be inferred that their optic condition was probably of vascular etiology In the literature optic neuritis of vascular pathognesis has been variously termed arteriosclerotic papillitis opticomalacia vascular pseudo papillitis or papillary apoplexy (Cogan 1968 Walsh & Hoyt 1969) It has been argued that they frequently appear as papillitis and that the prognosis for sight is poorer than for retrobulbar neuritis/papillitis seen in younger age groups It seems apparent from Tables IV and V that optic papillitis is rather more frequent in older patients than in a younger group The prognosis for sight appears to be the same for papillitis as for retrobulbar neuritis In the present material the prognosis for sight was poor in the higher age group but not as poor as reported in other studies (Cogan 1968 Walsh & Hoyt 1969) The prognosis for life was reduced in our patients with optic neuritic/papillitis appearing in the 7th decade 5 out of 7 patients died within 6 years of commencement of the optic condition corresponding to an average reduction of life expectancy of 10 years (Table III)

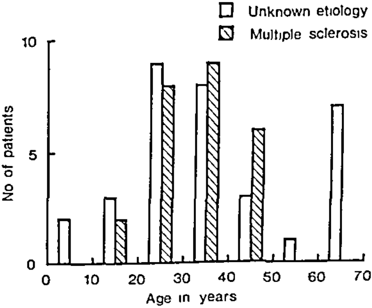


Fig 1
Age distribution in patient population

Table III

Patients who have died prior to the follow up investigation

Sex	Age	Life expectancy at time of onset of disease	Life span after optic disease	Difference	Cause of Death
Male	34	40 1	4 9	35 2	Suicide
Male	37	37 3	5 1	[illegible]	Mors subita sclerosis multiplex
Male	61	16 8	3 5	13 3	Apoplexia cerebri bronchopneumonia
Female	64	14 1	2 9	11 2	Infarctus cordis insuff cordis diabetes mellitus
Male*	6[illegible]	14 1	5 9	8 2	Vit org cordis
Male	6[illegible]	15 4	4 6	8 8	*hæmatemesis* bronchiectasis
Male	67	12 8	4 8	8 0	Apoplexia cerebri *bronchopneumonia*

* The same patient He had a remission one year after the initial episode

Table IV

Prognosis for sight in relation to initial reduction in visual acuity in patients below 60 years of age

Initial impairment of visual acuity	6/6–6/8 5		6/9–6/18		6/20–6/60		6/60 or less	
	N	P	N	P	N	P	N	P
Visual acuity improved to								
6/6–6/8 5	7		8		6	2	13	8
6/9–6/18						1		
6/20–6/60			1				2	
6/60 or less					1		1	

N = Retrobulbar neuritis
P = Optic papillitis

Taub & Rucker 1954) 7 patients comprise the 7th decade group in the present material Only 2 are alive The other 5 have died either from cardiovascular causes or secondary to such causes as apparent from Table III It may be inferred that their optic condition was probably of vascular etiology In the literature optic neuritis of vascular pathognesis has been variously termed arteriosclerotic papillitis opticomalacia vascular pseudo papillitis or papillary apoplexy (Cogan 1968 Walsh & Hoyt 1969) It has been argued that they frequently appear as papillitis and that the prognosis for sight is poorer than for retrobulbar neuritis/papillitis seen in younger age groups It seems apparent from Tables IV and V that optic papillitis is rather more frequent in older patients than in a younger group The prognosis for sight appears to be the same for papillitis as for retrobulbar neuritis In the present material the prognosis for sight was poor in the higher age group but not as poor as re ported in other studies (Cogan 1968 Walsh & Hoyt 1969) The prognosis for life was reduced in our patients with optic neuritic/papillitis appearing in the 7th decade 5 out of 7 patients died within 6 years of commencement of the optic condition corresponding to an average reduction of life expectancy of 10 years (Table III)

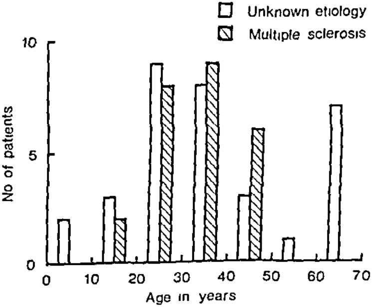


Fig 1

Age distribution in patient population

Aus der Univ Au enklinik Greifswald
(Direktor Professor Dr G Gunther)

UNTERSUCHUNGEN ZUR METHODIK EINER DYNAMISCHEN PUPILLOGRAPHIE

VON

G KIETZMANN und H GLIEM

Bericht uber eine pupillographische Untersuchungsmethodik auf photo elektrischer Basis die auch Amplitudenmessungen des Reflexablaufes ge stattet Durch elektronische Steuerung lassen sich Doppel und Flimmer belichtungen ausfuhren so dass das dynamische Reizantwortverhalten des pupillomotorischen Systems auf vielfaltige Weise untersucht werden kann

Key words pupillography – flicker

Die Untersuchung eines rasch reagierenden und vielseitig beeinflussbaren Vor ganges wie des pupillomotorischen Regulationssystems und eine exakte Be urteilung seiner pathologischen Abweichungen erfordern eine hinreichend genaue objektive Registrierung Daruber hinaus erscheint es notwendig mit Hilfe variabel gestalteter Reizformen und intensitaten eine moglichst grosse Zahl von Informationen uber die Kenngrossen dieses Systems zu erlangen da eine Einzelantwort noch keine genugende Übersicht uber dessen Reaktions breite vermittelt Wir suchten daher nach einer *klinisch anwendbaren* (und deshalb auch okonomisch zu vertretenden) Methodik die uns eine objektive Aufzeichnung der Pupillodynamik und statik erlaubt Sie sollte gleichzeitig

Eingegangen Juli 25 1971

Table V

Prognosis for sight in relation to initial reduction in visual acuity in patients above 60 years of age

The table includes 7 patients with 8 affected eyes One of the patients had a binocular affection which was considered of non toxic nature as he had a monocular relapse

Initial impairment of visual acuity	6/6–6/8 5		6 9–6/18		6/20–6/60		6 60 or less	
	N	P	N	P	N	P	N	P
Visual acuity improved to								
6/6–6/8 5	1							2
6/9–6/18			1					2
6/20–6/60								
6/60 or less							1	1

N = Retrobulbar neuritis
P = *Optic papillitis*

References

Bardram M & Moller H V (1952) Diagnosis of tumours in anterior and middle cranial fossae *Acta ophthal (Kbh) 30* 65–95

Gibis P (1939) Über die Aetiologie und Haufigkeitsverhaltnisse der Neuritis retro bulbaris *Klin Mbl Augenheilk 102* 205–223

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Fleischer B (1908) Neuritis retrobulbaris acuta und multiple Sclerose *Klin Mbl Augenheilk 1* 113–140

Hyllested K (1950) Neuritis retrobulbaris og dissemineret sclerose *Ugeskr Læg* 853–865

Hyllested K & Moller P M (1961) Follow up on patients with a history of optic neuritis *Acta ophthal (Kbh) 39* 655–662

Larsson S & Nord B (1947) Klinisk bild av retrobulbarneurit vid intrakraniella tumorer *Nord Med 34* 1059–1065

Taub R G & Rucker C W (1954) The relationship of retrobulbar neuritis to multiple sclerosis *Amer J Ophthal 37* 494–497

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VON

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Die Untersuchung eines rasch reagierenden und vielseitig beeinflussbaren Vor ganges wie des pupillomotorischen Regulationssystems und eine exakte Be urteilung seiner pathologischen Abweichungen erfordern eine hinreichend genaue objektive Registrierung Darüber hinaus erscheint es notwendig mit Hilfe variabel gestalteter Reizformen und intensitäten eine möglichst grosse Zahl von Informationen über die Kenngrossen dieses Systems zu erlangen da eine Einzelantwort noch keine genügende Übersicht über dessen Reaktions breite vermittelt Wir suchten daher nach einer *klinisch anwendbaren* (und deshalb auch ökonomisch zu vertretenden) Methodik die uns eine objektive Aufzeichnung der Pupillodynamik und statik erlaubt Sie sollte gleichzeitig

Eingegangen Juli 23 1971

Table V

Prognosis for sight in relation to initial reduction in visual acuity *in patients above* 60 years of age.

The table includes 7 patients with 8 affected eyes One of the patients had a binocular affection which was *considered of non toxic nature as he had a monocular relapse*

Initial impairment of visual acuity	6/6–6/8 5		6/9–6/18		6/20–6/60		6/60 or less	
	N	P	N	P	N	P	N	P
Visual acuity improved to								
6/6–6/8 5	1							2
6/9–6/18			1					2
6/20–6/60								
6/60 or less							1	1

N = *Retrobulbar neuritis*
P = Optic papillitis

References

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UNTERSUCHUNGEN ZUR METHODIK EINER DYNAMISCHEN PUPILLOGRAPHIE*

VON

G. KIETZMANN und H. GLIEM

Bericht über eine pupillographische Untersuchungsmethodik auf photoelektrischer Basis, die auch Amplitudenmessungen des Reflexablaufes gestattet. Durch elektronische Steuerung lassen sich Doppel- und Flimmerbelichtungen ausführen, so dass das dynamische Reizantwortverhalten des pupillomotorischen Systems auf vielfältige Weise untersucht werden kann.

Key words: pupillography – flicker

Die Untersuchung eines rasch reagierenden und vielseitig beeinflussbaren Vorganges wie des pupillomotorischen Regulationssystems und eine exakte Beurteilung seiner pathologischen Abweichungen erfordern eine hinreichend genaue objektive Registrierung. Darüber hinaus erscheint es notwendig, mit Hilfe variabel gestalteter Reizformen und -intensitäten eine möglichst grosse Zahl von Informationen über die Kenngrössen dieses Systems zu erlangen, da eine Einzelantwort noch keine genügende Übersicht über dessen Reaktionsbreite vermittelt. Wir suchten daher nach einer *klinisch anwendbaren* (und deshalb auch ökonomisch zu vertretenden) Methodik, die uns eine objektive Aufzeichnung der Pupillodynamik und -statik erlaubt. Sie sollte gleichzeitig

Eingegangen Juli 23, 1971.

Untersuchungen über das Verhältnis von Reizintensität und Kontraktions amplitude über die Beziehungen zwichen Latenz und Kontraktionszeit unter dem Einfluss der Belichtungsstärke sowie die Beurteilung der Reaktion unter den Bedingungen von Flimmer und unterschiedlich gestalteten Doppelblitz reizen ermöglichen

Diese komplexe Untersuchungsweise des pupillomotorischen Systems haben wir zunächst als dynamische Pupillographie" bezeichnet Der eingeschlagene methodische Losungsweg und die ersten Ergebnisse einer Gruppe von ge sunden Versuchspersonen sollen geschildert werden

Das *vollelektronische Registrierverfahren* stand ausserhalb der uns gege benen Moglichkeiten Mit Hilfe der *kinematographischen Methode* (Loewen stein Dolenek) kann die Grossenänderung der Pupille direkt gemessen wer den sie ermöglicht aber die kontinuierliche Aufzeichnung des Reflexablaufes nicht ohne weiteres Das *photoelektrische Prinzip* (Matthes Drischel) ist da gegen sehr einfach anzuwenden gestattet aber zunächst nur Aussagen uber die Kinetik des Pupillenreflexes Die Beurteilung der Pupillenweite und ihrer Anderung sind hierbei nicht moglich

Eigene Untersuchungen

Wir machten uns den Vorteil des photoelektrischen Registrierverfahrens zu nutze und glichen den geschilderten Nachteil durch die Photographie der Pu pille vor und nach dem Lichtreiz aus Da sich hiermit die Gesamtamplitude der Iriskontraktion ausmessen lasst wurde uns ein Bezugssystem gegeben welches eine ausreichende Korrelation der kinetischen Verhältnisse mit der Ampli tudenänderung gestattet Die exakte Einhaltung der gesamten Versuchsanord nung ist dabei allerdings eine unerlassliche Voraussetzung

Der Messvorgang lasst sich wie folgt zusammenfassen

Zu Beginn der Untersuchung wird die Ausgangsweite der Pupille auf pho tographischem Wege registriert Danach wird durch einen Lichtreiz mit defi nierter Intensität spektraler Zusammensetzung und Dauer eine Kontraktion der Pupille ausgelost die auf photoelektrischem Wege durch den Direktschrei ber des EEG registriert wird Sodann wird die Gipfelzeit der Kontraktion be stimmt die aus Latenz und Kontraktionszeit besteht und diese an einem Zeitverzogerer des zur Photographie dienenden Blitzlichtes eingestellt Nach einem erneuten Lichtreiz kann auf diese Weise die Pupillenweite während des Kontraktionsmaximums erfasst werden Da die Dauer des Elektronen blitzes 1/500–1/1000 sec die Latenzzeit der Pupille aber um 0 2 sec beträgt

wird der Elektronenblitz erst nach Beendigung der photographischen Aufzeichnung pupillomotorisch wirksam

Nach Abschluss der weiter unten naher geschilderten Gesamtuntersuchung wird der Film entwickelt und das Ausmass der in diesen zwei Aufnahmen festgehaltenen Verengerung der Pupille gemessen Dieser Wert lasst sich mit allen photoelektrischen Registrierungen in Beziehung bringen Das Verfahren erlaubt somit die Grossenanderungen der Pupille bei genauer Zeitmessung zu bestimmen

Das Versuchsgerat besteht aus den Teilen zur Reizlichterzeugung zur photoelektrischen Registrierung und zur photographischen Messung der Pupillenweite

Beim Bau der *Einheit zur Rei lichter eugung* folgten wir den Empfehlungen von Cuppers (1951) and Drischel (1957) und benutzten die kleinstmogliche Pupillenoffnung (2 mm) als Mass fur die Grosse des Lichtbundels in der Iris ebene Hierdurch wird die intentitatsandernde Wirkung des Reflexes vermieden und eine stimulatorische Konstanz erziehlt Als Lichtquelle diente der Spaltlampenteil (6V/30W Gleichstrom) eines Hornhautmikroskops wobei dessen Kreuztisch einen raschen Seitenwechsel ermoglicht Die Variabilität der Reizdauer von 18 Stufen zwischen 100 msec und 2 sec gestattete ein selbstentwickelter elektromagnetischer Verschluss der durch einen elektronischen Zeitschalter betatigt wird Durch die Steuerung dieser Einheit zur Reizlichterzeugung mit dem Foto Fono Stimulator FS 4 (VEB TuR Dresden) uber einen monostabilen Multivibrator (Haltezeit 70 msec) erhielten wir die Moglichkeit Flimmerreize mit Rechteckimpulsen von 0 2 bis 6 Hz und Doppelsprunge mit grosser Variabilitat anzuwenden

Die Intensitat und spektrale Zusammensetzung des Reizlichtes kann durch Neutralglasfilter (10 % 1 % 0 1 % 0 01 %) sowie von Farbfiltern geandert werden

Die zwei Adapter der *photoelektrischen Einheit* sind schwenkbar zu beiden Seiten des Probanden an einer Kopfkinnstutze angebracht und werden wahrend des Untersuchungsvorganges auf die Irides gerichtet Sie bestehen aus Photodioden (Typ PHG 1 D) Infrarotfiltern RG 7/2 mm (VEB Schott & Gen Jena) und Lichtquellen (6V/5W) Der Photostrom der Dioden der durch das von den Irides reflektierte Infrarotlicht erzeugt wird wird durch einen direkt schreibenden 8 Kanal Elektroencephalographen (VEB WTBG) verstarkt und aufgezeichnet Angeschlossen ist ebenfalls ein Oszillograph (Duoskop Techn Phys Werkstatten Thalheim)

Die *photographische Einheit* besteht aus einem Photogerat (Exakta varex) einem Blitzlichtgerat (Elgapress Plauen) und dem Zeitverzogerungsschalter der selbst hergestellt wurde (Abb 1)

Untersuchungen über das Verhältnis von Reizintensität und Kontraktionsamplitude, über die Beziehungen zwischen Latenz- und Kontraktionszeit unter dem Einfluss der Belichtungsstärke sowie die Beurteilung der Reaktion unter den Bedingungen von Flimmer- und unterschiedlich gestalteten Doppelblitzreizen ermöglichen.

Diese komplexe Untersuchungsweise des pupillomotorischen Systems haben wir zunächst als „dynamische Pupillographie" bezeichnet. Der eingeschlagene methodische Lösungsweg und die ersten Ergebnisse einer Gruppe von gesunden Versuchspersonen sollen geschildert werden.

Das *vollelektronische Registrierverfahren* stand ausserhalb der uns gegebenen Möglichkeiten. Mit Hilfe der *kinematographischen Methode* (Loewenstein, Doleneck) kann die Grössenänderung der Pupille direkt gemessen werden, sie ermöglicht aber die kontinuierliche Aufzeichnung des Reflexablaufes nicht ohne weiteres. Das *photoelektrische Prinzip* (Matthes, Drischel) ist dagegen sehr einfach anzuwenden, gestattet aber zunächst nur Aussagen über die Kinetik des Pupillenreflexes. Die Beurteilung der Pupillenweite und ihrer Änderung sind hierbei nicht möglich.

Eigene Untersuchungen

Wir machten uns den Vorteil des photoelektrischen Registrierverfahrens zunutze und glichen den geschilderten Nachteil durch die Photographie der Pupille vor und nach dem Lichtreiz aus. Da sich hiermit die Gesamtamplitude der Iriskontraktion ausmessen lässt, wurde uns ein Bezugssystem gegeben, welches eine ausreichende Korrelation der kinetischen Verhältnisse mit der Amplitudenänderung gestattet. Die exakte Einhaltung der gesamten Versuchsanordnung ist dabei allerdings eine unerlässliche Voraussetzung.

Der Messvorgang lässt sich wie folgt zusammenfassen:

Zu Beginn der Untersuchung wird die Ausgangsweite der Pupille auf photographischem Wege registriert. Danach wird durch einen Lichtreiz mit definierter Intensität, spektraler Zusammensetzung und Dauer eine Kontraktion der Pupille ausgelöst, die auf photoelektrischem Wege durch den Direktschreiber des EEG registriert wird. Sodann wird die Gipfelzeit der Kontraktion bestimmt, die aus Latenz- und Kontraktionszeit besteht, und diese an einem Zeitverzögerer des zur Photographie dienenden Blitzlichtes eingestellt. Nach einem erneuten Lichtreiz kann auf diese Weise die Pupillenweite während des Kontraktionsmaximums erfasst werden. Da die Dauer des Elektronenblitzes 1/500–1/1000 sec, die Latenzzeit der Pupille aber um 0,2 sec beträgt,

wird der Elektronenblitz erst nach Beendigung der photographischen Auf zeichnung pupillomotorisch wirksam

Nach Abschluss der weiter unten naher geschilderten Gesamtuntersuchung wird der Film entwickelt und das Ausmass der in diesen zwei Aufnahmen festgehaltenen Verengerung der Pupille gemessen Dieser Wert lasst sich mit allen photoelektrischen Registrierungen in Beziehung bringen Das Verfahren erlaubt somit die Grossenanderungen der Pupille bei genauer Zeitmessung zu bestimmen

Das Versuchsgerat besteht aus den Teilen zur Reizlichterzeugung zur pho toelektrischen Registrierung und zur photographischen Messung der Pupil lenweite.

Beim Bau der *Einheit ur Rei lichter eugung* folgten wir den Empfehlungen von Cuppers (1951) and Drischel (1957) und benutzten die kleinstmogliche Pupillenoffnung (2 mm) als Mass fur die Grosse des Lichtbundels in der Iris ebene Hierdurch wird die intentitatsandernde Wirkung des Reflexes ver mieden und eine stimulatorische Konstanz erzielt Als Lichtquelle diente der Spaltlampenteil (6V/30W Gleichstrom) eines Hornhautmikroskops wobei des sen Kreuztisch einen raschen Seitenwechsel ermoglicht Die Variabilitat der Reizdauer von 18 Stufen zwischen 100 msec und 2 sec gestattete ein selbstent wickelter elektromagnetischer Verschluss der durch einen elektronischen Zeit schalter betatigt wird Durch die Steuerung dieser Einheit zur Reizlichter zeugung mit dem Foto Fono Stimulator FS 4 (VEB TuR Dresden) uber einen monostabilen Multivibrator (Haltezeit 70 msec) erhielten wir die Moglichkeit Flimmerreize mit Rechteckimpulsen von 0 2 bis 6 Hz und Doppelsprunge mit grosser Variabilitat anzuwenden

Die Intensitat und spektrale Zusammensetzung des Reizlichtes kann durch Neutralglasfilter (10 % 1 % 0 1 % 0 01 %) sowie von Farbfiltern geandert werden

Die zwei Adapter der *photoelektrischen Einheit* sind schwenkbar zu beiden Seiten des Probanden an einer Kopfkinnstutze angebracht und werden wahrend des Untersuchungsvorganges auf die Irides gerichtet Sie bestehen aus Photo dioden (Typ PHG 1 D) Infrarotfiltern RG 7/2 mm (VEB Schott & Gen Jena) und Lichtquellen (6V/5W) Der Photostrom der Dioden der durch das von den Irides reflektierte Infrarotlicht erzeugt wird wird durch einen direkt schreibenden 8 Kanal Elektroencephalographen (VEB WTBG) verstarkt und aufgezeichnet Angeschlossen ist ebenfalls ein Oszillograph (Duoskop Techn Phys Werkstatten Thalheim)

Die *photograpische Einheit* besteht aus einem Photogerat (Exakta varex) einem Blitzlichtgerat (Elgapress Plauen) und dem Zeitverzogerungsschalter der selbst hergestellt wurde (Abb 1)

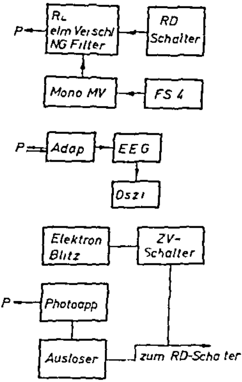


Abb 1
Blockschaltbild des Pupillographen mit den Einheiten zur Reizlichterzeugung zur photoelektrischen und photographischen Registrierung

Untersuchungsgang

Nach einer Voradaptation von 10 min bei ca 5 lux wird der Kopf des Probanden auf der Kinnstutze befestigt Bei Fernfixation wird die Ausgangsweite und anschliessend die nach dem Lichtreiz erzielte Verengerung photographisch registriert Nach dieser Festlegung des Bezugssystems kann jedes beliebige Untersuchungsprogram ausgeführt werden

Ergebnisse

Bei 10 Probanden wurden das Verhältnis zwischen Reizintensitat und der Kontraktionsamplitude zwischen Latenz und Kontraktionszeit sowie der Einfluss von Doppelblitz und Flimmerreizen auf die Kontraktionsamplitude der Pupille mit der beschriebenen Methodik untersucht

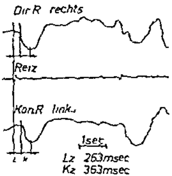


Abb 2

Originalkurven der direkten und konsensuellen Pupillenreaktion.

Die *Reaktion der Pupille auf kurze Lichtblitze unterschiedlicher Intensität* lässt sich mit Hilfe der beschriebenen Methodik sowohl hinsichtlich der Amplitudenänderung als auch der Kinetik ausreichend genau verfolgen Die Impulsantwort der Pupille setzt nach der Latenzzeit mit erheblicher Geschwindigkeit ein erreicht ihr Maximum und klingt danach ab um die Ausgangsweite

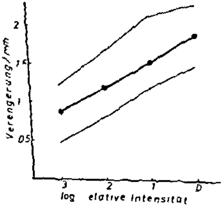


Abb 3

Abhängigkeit der durchschnittlichen Reizantwort von der Reizintensität.

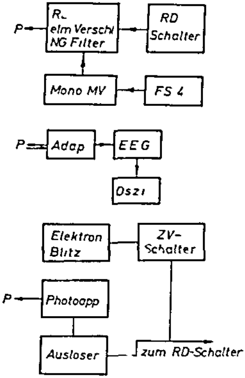


Abb 1
Blockschaltbild des Pupillographen mit den Einheiten zur Reizlichterzeugung zur photoelektrischen und photographischen Registrierung

Untersuchungsgang

Nach einer Voradaptation von 10 min bei ca 5 lux wird der Kopf des Probanden auf der Kinnstutze befestigt Bei Fernfixation wird die Ausgangsweite und anschliessend die nach dem Lichtreiz erzielte Verengerung photographisch registriert Nach dieser Festlegung des Bezugssystems kann jedes beliebige Untersuchungsprogram ausgefuhrt werden

Ergebnisse

Bei 10 Probanden wurden das Verhältnis zwischen Reizintensitat und der Kontraktionsamplitude zwischen Latenz- und Kontraktionszeit sowie der Einfluss von Doppelblitz und Flimmerreizen auf die Kontraktionsamplitude der Pupille mit der beschriebenen Methodik untersucht



R 70 msec
t 200 1500 msec
T 400 5000 msec

Abb. 5

Varianten einer Doppelblitzfolge

wieder zu erreichen. Die Verengerung geschieht schneller als die Wiedererweiterung (Abb. 2).

Unter den zuvor geschilderten Bedingungen – insbesondere der, dass die Eintrittsöffnung des Reizlichtes kleiner ist als die maximale Pupillenverengerung – stellten wir eine direkte Abhängigkeit der durchschnittlichen Reizantwort (Pupillenverengerung in mm Durchmesser) von der Reizintensität fest (Abb. 3 und Tab. 1). Während die Latenzzeit kontinuierlich mit der steigenden Reizstärke abnimmt, verkürzt sich umgekehrt die Kontraktionszeit (= Dauer der Verengerung vom Ende der Latenzzeit bis zum Maximum) im gleichen Masse, so dass die Summe beider (= Reaktionszeit) annähernd konstant bleibt (Abb. 4 und Tab. 1).

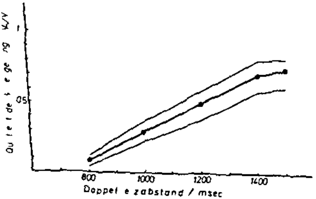


Abb. 6

Verhältnis der Verengerung V_2 zu V_1 in Abhängigkeit vom Doppelreizabstand

Tab 1

Werte der Intensitats Frequenz und Doppelreizabhangigkeit der Pupillenverengerung

Intens tatsabhang gke t der Pup llenverengerung					
	0	1	2	3	log relat in ens t
Ampl tude der Verengerung	23 18 14	21 13 11	16 1 06	,2 08 05	hochs er We t M ttelwert / mm t efste We t
Latenzzeit	233 206 193	280 2 7 2?0	320 2?6 226	338 3-3 293	msec
Kontraktions zeit	4-6 406 366	386 3-6 306	320 86 226	?53 ?0 80	mse

Frequenzabhangigke t der Pupi lenverengerung								
	0,2	05	10	15	20	25	30	Frequen. / Hz
Verengerung	2,2 2,0 1,1	2,1 18 1,5	18 1,2 09	13 0,7 0,5	0, 0,5 0,3	0,4 03 0,08	0,0'	mm

Verhaltnis der 2 (V_2) zur 1 (V_1) Verengerungsampl tude bei Doppe reizung						
	800	1000	1200	1400	1500	Intervall msec
V_2 / V_1	012 0,08 0,06	0,35 0,3 0,25	0,59 0,5 0, 1	0,8 07 0,6	0,83 0?5 0,63	

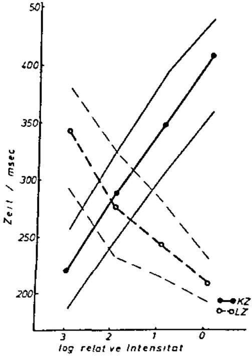


Abb 4

Verlauf der Latenz und Kontraktionszeit in Abhangigkeit von der relativen Intensitat

schen Regelkreis darstellt. Diese Betrachtungsweise ermoglicht nicht nur eine umfassendere Deutung physiologischer Eigenschaften sie muss zweifellos auch fur die Einordnung pathologischer Abweichungen genutzt werden Dieser mehr klinisch ausgerichteten Zielstellung sollte die Versuchsanordnung dienen Erste Ergebnisse uber die Pupillenstorungen bei Diabetikern sowie pharma kodynamische Untersuchungen bestatigen diese Auffassung

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Wird mit *zwei aufeinanderfolgenden gleich starken Lichtblitzen* gereizt so wird die Pupillenverengerung nach der zweiten Stimulation durch den Doppelblitzabstand bestimmt (Abb 5) Unterhalb einer Doppelblitzfolge von 800 msec konnte keine sichere Reaktion festgestellt werden Erst nach Überschreitung dieses Grenzwertes und stetiger Verlängerung des Intervalles wird eine zunehmende Vergrösserung der zweiten Antwort registriert Sie erreicht aber bei 1 5 sec noch nicht die Höhe der ersten (Abb 6 und Tab 1)

Unter *Flimmerbelichtung* mit Rechtecksprüngen wie sie durch die beschriebene Versuchsanordnung möglich war lässt sich die Frequenzabhängigkeit der Pupillenverengerung infolge des Wechsels zwischen Belichtung und Verdunklung ermitteln Während bei einer Folge von je 1 Blitz innerhalb von 5 sec noch eine Weitenänderung um durchschnittlich 2 mm festzustellen war nahm diese mit der Frequenzerhöhung der Stimulation fortlaufend ab Bei 3 Blitzen/sec blieb die Pupille reaktionslos Die 50 % Grenze wurde bei 1 Hz beobachtet (Abb 7)

Diese kurze Darlegung vorläufiger Ergebnisse sollte die Möglichkeiten der Versuchsanordnung illustrieren Neben der Impulsantwortprüfung und der geschilderten (unvollständigen) Frequenzganganalyse ist eine Erweiterung der Methodik in Richtung auf eine Untersuchung der Sprungantwort ohne technische Schwierigkeiten denkbar Damit ist eine Adaptation für systemtheoretische Untersuchungen gegeben Mit Erfolg konnte durch Drischel Stark u a der Nachweis geführt werden dass der Pupillarmechanismus nicht als Reflexbogen d h als offene Kausalkette betrachtet werden muss sondern eine zyklisch geschlossene Kausalkette mit negativem „feed back" einen biologi

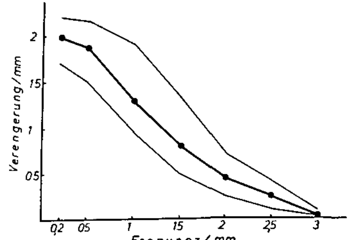


Abb 7

Beziehungen zwischen Pupillenverengerung und der Frequenz des Reizlichtes

Buffaloe 1960) keratopathy in human beings have been reported frequently However chlorpromazine keratopathy has not been reproduced in the experimental animal and only a single report of experimental chloroquine keratopathy (in rats) could be located (Francois & Maudgal 1965) Following long term chloroquine (Bernstein et al 1963 Dale et al 1965 McConnell et al 1964 Meier Ruge 1965) or chlorpromazine (Green & Ellison 1966 Potts 1962) loading experiments in animals there have been either no corneal effects or no reference to the cornea

Because of the photosensitive skin reaction of patients on long term chlorpromazine (Greiner & Berry 1964) and chloroquine (Tuffanelli et al 1963 Zacharie 1963) therapy the interpalpebral conjunctival pigmentation seen in patients on long term chlorpromazine treatment (Greiner & Berry 1964) the ability of chlorpromazine and chloroquine (Brodie et al 1947 Udenfriend 1962) to fluoresce in ultraviolet light (a property common to multiple photosensitizing drugs) and the inability to reproduce typical chloroquine and chlorpromazine keratopathy in the laboratory animal the possibility exists that the development of these drug induced keratopathies is actinic radiation dependent

It is the purpose of this paper to determine whether chronic ultraviolet light radiation in combination with long term treatment of the pigmented rabbit with chlorpromazine or chloroquine results in keratopathy

Methods

Six pigmented rabbits received chloroquine 40 mg (base)/kg I M while another six pigmented rabbits received chlorpromazine 4 mg/kg I M All *injections* were given three times weekly (Monday Wednesday and Friday) The rabbits initially weighed 1 6 3 3 kg Weighings were performed biweekly and appropriate changes were made in the dosage schedule Because two chloroquine rabbits died in convulsion in the sixth week of the experiment the chloroquine dosage was reduced to 30 mg (base)/kg and maintained at this level

For the first two months of the experiment August and September the animals were kept outdoors and exposed to sky radiation For the next five months the animals were kept indoors and exposed to ultraviolet radiation twice weekly from 1 30 p m until 9 00 a m The ultraviolet source blacklight consisted of a bank of eight 20 watt General Electric fluorescent lamps with a spectral range of 320–410 nanometers The lamps were initially calibrated without a filter at 10 inches The incident photon spectral intensity was 1460 microwatts/cm (equi

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THE EFFECT OF CHLOROQUINE CHLORPROMAZINE AND ULTRAVIOLET RADIATION ON THE CORNEAS OF PIGMENTED RABBITS

BY

JULES L BAUM

Following seven months of chloroquine or chlorpromazine administration in combination with chronic exposure to ultraviolet radiation chloroquine and chlorpromazine keratopathy could not be produced in the pigmented rabbit No measurable amounts of chloroquine or chlorpromazine were found in the experimental corneas The hypothesis that corneal changes seen in human beings following chloroquine or chlorpromazine therapy were unable to be reproduced in the laboratory animal because these changes were actinic radiation dependent was not borne out at least within the limits of this experiment

Key words chloroquine – chlorpromazine – ultraviolet radiation – cornea – rabbit

Introduction

Cloroquine (Calkins 1958 Greiner & Berry 1964 Hobbs & Calnan 1958 Hobbs et al 1961) and chlorpromazine (Cameron 1967 DeLong et al 1965 Johnson &

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throughout the seven month experimental period No evidence of conjunctival pigmentation or abnormal corneal deposits was seen at any time Occasional minor punctate staining with fluorescein was seen transiently and randomly in both the experimental animals and the controls and were considered not significant

The five corneas analyzed for chloroquine revealed no trace of the drug (< 0 20 µg)

In one animal the choroid and kidney were also analyzed for chloroquine and revealed 3 5 mg/gram (wet) and 0 214 mg/gram (wet) respectively

Fluorescence microscopy failed to reveal any trace of fluorescence over that of the normal autofluorescence of the controls

The thin layer chromatography plates revealed no trace of chlorpromazine from the corneas but did reveal a spot consistent with chlorpromazine from the liver Results are summarized in Table I

Discussion

The results of this study demonstrate that seven months of relatively high dose chloroquine or chlorpromazine treatment in combination with chronic exposure

Table I

Pigmented rabbit corneas following seven months of chronic loading with chloroquine or chlorpromazine

	Chloroquine	Chlorpromazine
Slit lamp findings following chronic ultraviolet radiation		
Experimental animals	normal	normal
Controls	normal	normal
Biochemical analysis		
Experimental animals	< 0 20 µg	< 1 µg
Control	3 5 mg/gram (choroid) 0 214 mg/gram (kidney	+ (liver)
Fluorescence microscopy		
Experimental animals	autofluorescence	
Controls	autofluorescence	

valent to 1.46×10^4 ergs/sec/cm.) The λ peak at 365 nanometers was equivalent to 2.68×10^{15} quanta/sec/cm. For the first three months a 1/8 inch glass filter was used and for the last two months a 300D mylar filter was used to cut off almost all ultraviolet light below 320 nanometers. Calibration of the incident photon spectral intensity with the glass filter revealed 840 microwatt/cm (equivalent to 8.20×10^3 erg/sec/cm) and 1100 microwatt/cm² (equivalent to 1.10×10^4 erg/sec/cm²) for the 300D mylar filter. The lamps were kept approximately 12 inches from the animals.

Injections were suspended on the Friday of three long weekends (Thanksgiving, Christmas and New Year's) and ultraviolet radiation and injections were suspended the week of January 22-29. Save for these exceptions the experiment continued uninterruptedly for seven months. Periodic slit lamp examinations of the rabbits were performed.

Corneas analyzed for chlorpromazine and chloroquine were excised just within the limbus immediately following a lethal intravenous pentabarbital injection.

Those corneas for chlorpromazine analysis were minced immediately following excision and analyzed according to the method of Davidow et al. (1966). This technique consists of acidified ethanol extraction, filtration and evaporation. The residues are then spotted on Silica Gel G thin layer chromotography plates with a solvent system of ethyl acetate-methanol-ammonium hydroxide. The plates are sprayed with methanol sulfuric acid.

Chloroquine extraction and purification were carried out by the method of Goldbaum & Williams (1959) and the identification and quantitation were performed by an ultraviolet spectrophometric method with specially adapted long light path cells (Goldbaum & Williams 1968).

Blocks of freshly excised cornea were embedded on edge in 7.5 per cent gelatin; the gelatin blocks were frozen in liquid nitrogen (Cooper 1967). Cryostat sections of the frozen blocks were mounted on glass slides, covered with Coons buffered glycerol mounting media (Coons & Kaplan 1950) and glass cover slips and examined under a Leitz Ortholux fluorescence microscope with a 2 mm UGI exciter and 2.5 mm Euphos barrier filter. A dark field condenser was employed.

Results

All pigmented rabbits, whether chlorpromazine or chloroquine loaded, whether exposed to ultraviolet light or not, maintained normal corneas and conjunctivae

diffuse stromal haze was noted in the corneas of a few animals Chlorpromazine 17 μg/gram (wet) was found in these experimental corneas after three months of treatment

The duration of this experiment seven months was selected based on clinical observations that both chloroquine and chlorpromazine keratopathy if they are to occur develop well within this time period (Hobbs et al 1961 Johnson & Buffaloe 1966) Also the dosage selected for both drugs was greater than the corresponding human dosage

Since the preceding experiments all varied as regards experimental animal analysis technique and amount time duration and route of drug administration the absence of chlorpromazine and chloroquine in the corneas of the present study and other studies cannot be commented upon Suffice it to say that if in the present study quantities of chlorpromazine and chloroquine were present in the cornea below the limits of detection with the methods employed the ultraviolet radiation did not produce either a chloroquine or chlorpromazine keratopathy

Acknowledgments

I would like to thank Mrs Grace Abel for her expert technical assistance Drs L Harber and J Hsu for supplying and calibrating the source of ultraviolet radiation Dr L Goldbaum for the chloroquine determinations Dr A Carella for the chlorpromazine determinations and Dr N Cooper for the fluorescence microscopy readings Smith Kline and French Laboratories and Winthrop Laboratories supplied the chlorpromazine and chloroquine respectively

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to ultraviolet radiation result in no observable slit lamp changes in the conjunctiva and cornea of the pigmented rabbit. Our original hypothesis that the corneal changes seen in human beings following chloroquine or chlorpromazine therapy could not be reproduced in the laboratory animal because these changes were actinic radiation dependent was not borne out, at least within the limits of this experiment.

Cogan & Kinsey (1946) have shown that threshold keratitis effects in rabbits are seen between 240-305 nanometers with a peak effect at 288 nanometers. We therefore used the glass and 300D mylar filters to cut off ultraviolet light below 320 nanometers. No corneal epithelial keratitis effects from the blacklight radiation were noted. Since chloroquine and chlorpromazine keratopathy did not develop, the possibility exists that ultraviolet radiation below 320 nanometers is a necessary stimulus for its production.

The failure to reproduce chloroquine and chlorpromazine keratopathy in this experiment might be explained in that neither chloroquine nor chlorpromazine was biochemically identified in the cornea nor was chloroquine demonstrated by fluorescence microscopy. These findings are in accord with some and in discord with other past experiments. Bernstein et al. (1963) found 62 gamma of chloroquine in four corneas of pigmented rats following six months of oral chloroquine administration. Baumer et al. (1959) and Francois & Maudgal (1965) demonstrated corneal epithelial fluorescence in animals on long term chloroquine while Pau & Baumer (1959) showed similar fluorscence in patients on long term chloroquine therapy. These fluorescence studies were performed after the corneas were exposed 20-40 minutes to ultraviolet radiation. In the present study, the corneas were not exposed to U.V. light immediately prior to fluorescence microscopy examination. We did note, however, a strong epithelial autofluorescence in both the experimental and control corneas. The aforementioned authors (Baumer et al. 1959, Francois & Maudgal 1965, Pau & Baumer 1959) do not indicate whether controls were used. Potts (1962) in S^{35} radioactive chlorpromazine studies found 0.18 $\mu g/gm$ wet weight in the cornea of pigmented rabbits two days after a single dose administration of the drug. After 80 days 0.05 $\mu g/gm$ remained. Rutschmann et al. (1962) in C^{14}, S^{35}, H^{3} radioactive studies found chlorpromazine in the cat and rabbit cornea 4 and 24 hours following drug administration. However, Green & Ellison (1966) using S^{35} chlorpromazine in albino and pigmented rabbits and dogs found no trace of the drug (<0.025-0.15 mg) in the cornea after four weeks of oral administration. Howard et al. (1969) exposed chlorpromazine loaded albino and pigmented guinea pigs to ultraviolet radiation over a period of 12 months. Although their main focus of attention was on the production of cataractous changes, they observed no significant corneal changes in their study. They do note, however, that a faint

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glaucoma there obviously being differences concerning choice from surgeon to surgeon or from one school to another

Generally nevertheless each surgeon usually chooses either that particular technique by which he himself has obtained the best results or the technique recommended in literature

But there are quite a number of cases in which the surgery of glaucoma does not achieve the expected results although the operation was technically correctly performed and the type of surgery chosen was the one indicated in the form of glaucoma in question This can be easily explained by taking into consideration the fact that the exact way in which glaucoma surgery works is not yet clearly known and understood

This is why some authors have tried to combine the different surgical procedures with one another thus performing simultaneous operations on the same eye In this may iridectomy has been combined with cyclodialysis or fistulizing operations with cyclodialysis

Simultaneous iridectomy and cyclodialysis was first performed in 1936 by Blaskovics Chandler & Morton (1966) used the same procedure in acute closure angle glaucoma with peripheral anterior synechiae involving more than one third of the angle circumference

Becker & Shafer (1965) are indicating the same operation in aphakic glaucoma with pupillary block

We began to perform this operation in 1962 and the technique we used was the following

1 Execution of a conjunctival flap with its base on the limbus in the inferior temporal quadrant with incision of the conjunctiva at 8 mm from the limbus

2 Incision of the sclera on a length of approximately 5 mm parallel to the limbus at a distance of 4 mm until the choroid is visible

3 Ordinary peripheral iridectomy ab externo at the superior limbus followed by the suture of conjunctiva with 5 0 plain catgut

4 Execution of classical cyclodilysis through the scleral incision prepared in advance

5 Introduction of air into the anterior chamber through the cyclodialysis channel

6 Suture of conjunctival flap

In some cases we injected a solution of hydrocortisone into the anterior chamber through the cyclodialysis channel

We have used the above technique on a total 54 eyes but we have only been able to follow up on 46 The periods of follow up are of 3 to 9 years

Eye Department "Donolo" Governmental Hospital Jaffa Tel Aviv and the Eye Department Central Polyclinic Workers Sick Fund Tel Aviv

PERIPHERAL IRIDECTOMY AND CYCLODIALYSIS AS SIMULTAENOUS OPERATION IN GLAUCOMA SURGERY

BY

M ROMEM & M PASCO

Peripheral iridectomy and cyclodyalisis as simultaneous operations were performed on 46 eyes with different clinical forms of glaucoma Normalisation of eve tension was obtained in 41 eyes (89 1 per cent) Postoperative complications were minimal (3 iritis and 1 hypotony)

Key words glaucoma surgery

The surgery of glaucoma consists in numerous surgical techniques which for all practical purposes can in fact be reduced to four important procedures

1 Excision of a part of the iris (iridectomy)

2 Creation of a fistula between the anterior chamber and the subconjunctival space (filtering operations)

3 Creation of a fistula between the anterior chamber and the suprachoroidian space by disinsertion of the ciliary body (cyclodialysis)

4 Reduction of the function of a part of the ciliary body (cyclodiathermy cyclocryotherapy or cycloanemisation)

Each of the above procedures is usually used in certain clinical forms of

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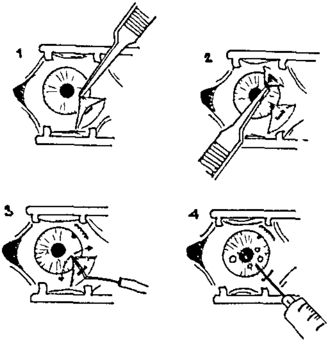


Fig 1
Steps in surgical technique of simultaneous iridectomy and cyclodialysis

Of the above 46 eyes 16 suffered from open angle glaucoma 15 from narrow angle glaucoma and 15 from acute angle closure glaucoma

Indications for surgery

We have used the above technique in quite a wide variety of cases but the number of interventions performed is still too small to allow us to draw precise and absolute conclusions on the indications for this surgical technique But we obtained excellent results in the following cases

1 In open and narrow angle glaucoma

(a) With very constricted visual field but good central vision

(b) With iris atrophy

(c) When a filtering operation previously performed on the other eye did not achieve satisfactory results

(d) When the other eye had been lost following surgery

2 In acute angle closure glaucoma

(a) When after the normalisation of intraocular tension by means of con servative treatment the pupil remained enlarged

(b) When in spite of decrease of the intraocular tension the – c – coefficient in tonography remained reduced

(c) When after discontinuing Diamox treatment the tension rose again.

3 In 6 cases when it was the patient s only eye

4 In 9 patients we applied this technique on the second eye after having previously used it successfully on the first eye

5 In glaucoma following thrombosis of the central retinal vein

Results

To appreciate the results we checked the patients periodically over an interval of time of 3 to 9 years We checked intra ocular tension visual field vision and gonioscopy

Intra ocular tension returned to normal in 41 eyes In 5 the tension did not return to normal and further surgery was necessary

Of the 41 eyes in which tension returned to normal treatment with miotics was not necessary in 22 in 19 eyes the instillation of miotics was necessary

It is interesting to note that the highest percentage of return to normal of the intraocular tension without the use of miotics was obtained in the cases of acute angle closure glaucoma (Table I)

The visual field remained unchanged in 29 cases and narrowed in 5 cases although the tension was back to normal In the other patients we were unable to appreciate the state of the visual field either owing to lack of cooperation on the side of the patient or because the visual field had not been examined before surgery

Vision remained unchanged in 29 eyes and diminished in 8 Cataract ap peared in the remaining 9 eyes (after one year in 2 eyes after 3 years in 3 eyes and after 3 to 8 years in 4 eyes)

Gonioscopy could be followed up in 24 patients only What particularly interested us was whether the cyclodialysis cleft remained open or not and what the relation was between the open cleft and ocular tension

Of the 4 eyes on which we were able to perform gonioscopy we found the cleft open in 18 and closed in 6 Of the 18 eyes with open cleft tension re

Table I

Intraocular tension in 46 eyes following simultaneous iridectomy and cyclodyalysis

	No of eyes	Normalised tension		Not normalised tension
		without treatment	with treatment	
Open angle glaucoma	16	6	8	2
Narrow angle glaucoma	15	5	8	2
Acute closure angle glaucoma	15	9	5	1
TOTAL	46	20	21	5

Table II

Intraocular tension in 24 eyes following simultaneous iridectomy and cyclodyalysis related to open or closed cleft

	No of eyes	Normalised tension	
		without treatment	with treatment
Open cleft	18	9	9
Closed cleft	6	–	6
TOTAL	24	9	15

turned to normal without miotics in 9 cases and with miotics in the other 9 In all 6 eyes in which the cleft appeared to be closed the tension could nevertheless be kept down to normal with miotics (Table II)

To facilitate maintaining the cleft open in some of the cases we operated on we introduced hydrocortisone solution through the cleft at the end of the

operation It may have been just a lucky coincidence but the cleft remained open in all these cases

Complications following surgery

Complications during or immediately following surgery were minimal In some cases a limited haemorrhage occurred in the anterior chamber but it resorbed in a few days

During the first week mild iris reaction was observed in 13 cases In 3 cases iritis appeared after surgery Inflammatory phenomena in the iris disappeared in all cases after a few days of local corticosteroid treatment

Hypotony appeared in one eye but this problem too was easily solved One patient developed malignant glaucoma following the operation and surgery was again required

In none of the cases did delayed infection appear throughout the observation period

The only delayed complication we ought the mention is cataract Cataract appeared in 9 of our 46 eyes (19 5 per cent) In 2 patients cataract was detected in the first year following the operation in 3 after 3 years and in 4 between 3 and 8 years after the operation

It is very hard to say whether the cataract was really a consequence of surgery or whether it was caused by the lengthy treatment with miotics or lastly whether it was just a case of ordinary senile cataracts without any connection whatsoever with the glaucoma (taking into consideration that the average age of the patients who underwent surgery was 60)

Conclusions

Analysing the results obtained by means of a surgical technique of *simultaneous* glaucoma operation of concomitent peripheral iridectomy and cyclodialysis on 46 eyes one can make the following remarks

1. The return to normal of ocular tension achieved by surgery in 41 cases (22 without and 19 with *miotics*) as well as a very low *percentage* of complications following surgery *prove* that the simultaneous operation is an operation involving no more risk than ordinary glaucoma surgery

2 It is very hard to explain exactly how the simultaneous operation works and which of the two mechanisms has a greater positive influence on the favourable post operative evolution of the glaucoma The fact that the best post operative results were obtained in acute angle closure glaucoma could lead us to suspect that the peripheral iridectomy was the one that had the greater influence

As the positive results obtained in the cases of narrow angle and open angle glaucoma cannot be neglected either we must be satisfied with appreciating the results obtained without being able to explain the exact mechanism by which they were achieved

3 The percentage of cataract after surgery (19 5 per cent) is very satis factory indeed it being not higher than that mentioned by other authors after ordinary glaucoma surgery

4 An advantage of this technique is the fact that in case of renewed ocular tension, filtering iridectomy or perhaps cyclodialysis in another quadrant can still be performed

5 Although the simultaneous operation is not an ordinary one we believe it should be taken into consideration in certain cases of glaucoma

Acknowledgement

We are grateful to Dr N Goldstein for her help in preparing this paper

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SOME FACTORS AFFECTING THE DISTRIBUTION OF INTRAOCULAR PRESSURES IN A POPULATION

BY

BO BENGTSSON

The rise in ocular tension with age is dependent on a concomitant rise in systemic blood pressure Sex season time of day and systemic blood pressure have independent effects on the distribution of applanation pressures in a population but are to the best of our knowledge not associated with glaucoma Their combined effects are large enough to support the opinion that they should be taken into account when evaluating the results of applanation tonometry

Key words applanation pressure – population study – multiple regression – systemic blood pressure – age – sex – season – time of day

Increasing numbers of patients with ocular tension greater than the accepted normal limit are detected as a result of routine tonometry and glaucoma screening Until recently all such cases were treated immediately Now there is evidence that untreated ocular hypertension has a favourable prognosis far

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more often than assumed before (Linnér & Strömberg 1967, Nörskov 1970) but there are still no reliable methods to identify those individuals who eventually will develop visual field defects (Armaly 1969).

In this situation any possibility of reducing the number of false positive cases should be seriously considered. One approach is suggested by the fact that the distribution of applanation pressure readings in an unselected population is affected by factors that are not associated with glaucoma. Consequently the use of a single pressure level as an index of suspicion causes persons of certain categories to be classified as glaucoma suspects with less justification than others. A detailed analysis of the normal variations in ocular tension is a prerequisite to progress in this field.

Previous workers have stressed the variations with age. Armaly (1967) described "a method of converting the applanation pressure into a standard score which is independent of age and sex." Graham & Hollows (1964) state that "the effects of diurnal variations and the age effect are important when comparing measurements of groups of people" and Pollack (1968) in a review of glaucoma screening considers "a breakdown of the screening level by age" to be useful.

More recently new sources of variation have been introduced and the present study was undertaken in order to assess the importance of various factors believed to affect the intraocular pressure, presuming that some of them should be taken into account when evaluating the results of tonometric measurements.

Material

The material is derived from a general ophthalmic survey which was carried out at *the Dalby Health Center in southern Sweden from March 1969 to April 1970*.

An invitation with a brief questionnaire was mailed to all persons aged 8 years or more and living in the village surrounding the Health Center since December 1968. Out of 1917 persons invited 1702 (88.8 per cent) took part in the study.

Reliable applanation readings were obtained in 1644 cases. Their age and sex distribution is given in Table I. 20 patients subject to antiglaucomatous treatment (eight cases), lesions in the anterior chamber angle (six cases), active uveitis (four cases) or glaucomatous field defects (two cases) were excluded from parts of the investigation intended to describe the normal variations in ocular tension (Results I, II and III).

Even in the highest age group the response rate was over 80 per cent but 215 persons – 127 males and 88 females – failed to appear 25 referred to illnesses 23 considered themselves prevented in other ways and 136 simply refused No response was received from 31 individuals Information on the eye condition was obtained in 136 cases not one of which was treated or observed for glaucoma or ocular hypertension

Applanation tonometry was impossible or unreliable in 58 cases – 23 males and 35 females – because of faints (nine cases) ocular diseases unrelated to glaucoma (eight cases) or unsatisfactory cooperation (41 cas s most of them old people or small girls)

Table 1

Number of men and women invited and applanated in different age groups

Age (years)	Men			Women		
	Invited No	Applanated		Invited No	Applanated	
		No	Per cent		No	Per cent
8–9	48	45	94	4[illegible]	38	84
10–1[illegible]	160	137	86	147	1[illegible]7	86
[illegible]0–[illegible]9	158	1[illegible]4	[illegible]8	1[illegible]6	1[illegible]0	90
30–39	179	15[illegible]	87	172	159	92
40–49	141	116	8[illegible]	13[illegible]	11[illegible]	8[illegible]
50–[illegible]9	107	93	87	102	93	91
60–[illegible]9	95	84	8[illegible]	97	8[illegible]	88
[illegible]0–[illegible]9	48	39	81	74	59	80
80–	18	11	61	28	17	61
Total	954	804	84	963	840	87

Methods

Visual acuity ophthalmometry slit lamp examination applanation tonometry Schiotz tonometry sphygmomanometric measurement of the systemic blood pressure ophthalmoscopy in mydriasis subjective refraction in cycloplegia and fundus photography were all attempted in every case by the same person using conventional equipment according to a fixed program

The data were immediately codified and recorded on special forms Transfer to punch cards and further treatment were performed at the Computer Center in Lund

As a rule right and left eyes have been analysed separately The arithmetic mean and the standard deviation were used to describe the pressure distributions Simple curves of regression were plotted in order to facilitate selection of suitable transgenerations of variables A multiple regression analysis was carried out with two BMD computed programs – 02R and 03R (Dixon 1970) – by way of exception using the arithmetic mean of the applanation readings on the two eyes to represent the intraocular pressure of the individual

The intraocular pressure was measured by an ophthalmologist using a Goldmann applanation tonometer mounted on a Haag Streit 900 slit lamp The tonometer was tested at *Physikalisch Technischen Bundesanstalt in Berlin* and found *to be* completely devoid of demonstrable errors in the normal pressure range For method see Jessen (1969)

Tepid Novesin 0 4 per cent was instilled twice followed by an ample dose of fluorescein from selected batches of Haag Streit fluorescein paper applicators

Much effort was spent reassuring the patients in order to secure optimal cooperation *When comfortably seated each subject was asked to relax to breathe as usual* to maintain both eyes widely open and to look towards a wall 5 meters in front The right eye was always measured first the instrument was read to the nearest millimeter and the first reliable reading was recorded

As a rule only one reading was needed Some patients were however not able to cooperate perfectly until the first trial had convinced them that the procedure was painless and a second reading taken a few seconds later was often several millimeters lower than the first In such cases the second reading was used This situation was always suspected when the reading on the left eye was more than two millimeters lower than that on the right eye It was felt that the best estimate of the pressure in the undisturbed eye was obtained in this way

The systolic and diastolic blood pressures were measured on the right arm with the patient remaining in a recumbent position after Schiotz tonometry by a nurse using a mercury manometer read to the nearest 5 mm Hg inflatable arm cuffs of different sizes and a stethoscope

Results

There were no significant differences between the two eyes (Table II) The figures are based on observations on the right eye

1 Variations in mean intraocular pressure

a *Simple correlations*

As expected women had somewhat higher applanation readings than men (Table II) Persons measured in the morning had generally greater ocular

tension than those measured in the evening (Fig 1) The mean pressure was higher during the winter than in the summer (Fig 2) The changes in intra ocular pressure with age are shown in Fig 3 We found however that the applanation pressure was far more strongly associated with systemic blood pressure than with any other tested variable There was a rather steep and almost linear rise with both systolic (Fig 4) and diastolic blood pressure as well as with the average blood pressure and the systolic – diastolic difference

It should be appreciated that the blood pressures are higher among older people that we measured more men than women in the evenings and that people living in districts

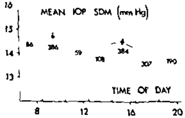


Fig 1
Change in mean applanation pressure (ordinate) with independent variable (abscissa) The circles represent the mean the vertical lines one standard deviation of the mean above and below the mean and the numbers the number of observations in each class

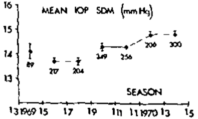


Fig 2
For legend see Fig 1
(Note that 1/3 means March 1st etc)

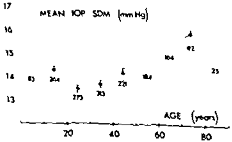


Fig 3
For legend see Fig 1

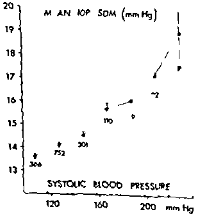


Fig 4
For legend see Fig 1

Table II

Pressures in subsamples of the population

	Intraocular pressure		Residual pressure*	
	Mean ± one standard deviation (number of observations) mm Hg			
	Right eye	Left eye	Right eye	Left eye
8 – 9 years	14.4 ± 2.26 (83)	14.6 ± 2.12 (83)	0.65 ± 2.23 (82)	0.81 ± 2.04 (82)
10 – 19 years	14.3 ± 2.27 (264)	14.5 ± 2.28 (262)	0.35 ± 2.23 (261)	0.50 ± 2.24 (260)
20 – 29 years	13.5 ± 2.23 (273)	13.7 ± 2.21 (273)	–0.46 ± 2.18 (273)	–0.35 ± 2.15 (273)
30 – 39 years	13.7 ± 2.39 (313)	13.8 ± 2.39 (312)	–0.24 ± 2.31 (312)	–0.18 ± 2.31 (311)
40 – 49 years	14.2 ± 2.70 (221)	14.2 ± 2.59 (221)	0.05 ± 2.54 (221)	0.10 ± 2.44 (221)
50 – 59 years	14.5 ± 2.51 (184)	14.5 ± 2.66 (184)	–0.23 ± 2.36 (182)	–0.21 ± 2.51 (182)
60 – 69 years	15.4 ± 3.20 (164)	15.4 ± 2.86 (165)	0.22 ± 2.98 (162)	0.27 ± 2.63 (163)
70 – 79 years	15.9 ± 3.24 (92)	15.8 ± 2.83 (91)	0.28 ± 3.03 (92)	0.20 ± 2.66 (91)
80 – 89 years	15.1 ± 2.26 (25)	15.4 ± 2.33 (25)	–0.67 ± 2.20 (24)	–0.34 ± 2.43 (24)
90 – 99 years	14.0 ± 0.00 (2)	14.0 ± 1.41 (2)	–2.80 ± 0.14 (2)	–2.80 ± 1.56 (2)
Not treated with diuretics	14.2 ± 2.60 (1561)	14.3 ± 2.53 (1558)	–0.03 ± 2.45 (1551)	0.05 ± 2.38 (1549)
Treated with diuretics	15.8 ± 2.67 (60)	15.8 ± 2.60 (60)	0.09 ± 2.40 (60)	0.07 ± 2.40 (60)
Males	13.9 ± 2.51 (797)	14.0 ± 2.46 (795)	–0.08 ± 2.42 (793)	0.01 ± 2.37 (792)
Females	14.6 ± 2.67 (824)	14.7 ± 2.57 (823)	0.02 ± 2.47 (818)	0.08 ± 2.39 (817)
Total	14.3 ± 2.62 (1621)	14.4 ± 2.54 (1618)	–0.03 ± 2.45 (1611)	0.05 ± 2.38 (1609)

* Residual pressure = Difference between measured IOP and expected IOP
the expected IOP being derived from a modified multiple regression equation

surveyed in winter months were (by chance) of more than average age In order to be able to assess the relative significance of the various factors it was therefore necessary to perform a multiple regression analysis

b *Multiple correlations*
We used a standard programme (BMD 0?R) to compute a sequence of multiple linear regression equations in a stepwise manner At each step the variable which had the highest partial correlation with the dependent variable (partialed on the variables already added) was added to the regression equation

The partial correlations of other blood pressure parameters with the intra ocular pressure were abolished as soon as the systolic blood pressure was added to the regression equation The changes in ocular tension with sex season time of day and systolic blood pressure remained largely undiminished and could not be accounted for by correlations with any tested independent vari able No linear effects of age were left when the influences of sex season time of day and systolic blood pressure were allowed for (Table III)

A number of multiple regression analyses (BMD 03R) within suitable subsamples of the population showed that the effects on the intraocular pres sure of the four remaining variables (sex season time of day and systolic blood pressure) were largely independent of each other even if a minor inter action between sex and season could be suspected in the present material the seasonal effect being greater in women

II Variations in dispersion of intraocular pressure

The four variables which affected the mean had no systematic effect on the dispersion of applanation readings There was however a tendency towards higher standard deviations in the higher age groups (Table II)

The intraocular pressures in different ages from 8 to 64 years were very nearly normally distributed as judged from plots of the cumulative per cent frequency on a probability scale Between 65 and 79 years of age very high values were overrepresented but the main part of the frequency distribution curve had the same form and width as that of younger people (Fig 5)

It was concluded that the standard deviation did not give an adequate description of the variations in dispersion with age

III Correction of applanation pressure

So far available data indicated that a simple but reasonably accurate descrip tion of the observed variations in distribution of intraocular pressure in the

Table II

Pressures in subsamples of the population

	Intraocular pressure		Residual pressure*	
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	Right eye	Left eye	Right eye	Left eye
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20 – 29 years	13.5 ± 2.23 (273)	13.7 ± 2.21 (273)	–0.46 ± 2.18 (273)	–0.35 ± 2.15 (273)
30 – 39 years	13.7 ± 2.39 (313)	13.8 ± 2.39 (312)	–0.24 ± 2.31 (312)	–0.18 ± 2.31 (311)
40 – 49 years	14.2 ± 2.70 (221)	14.2 ± 2.59 (221)	0.05 ± 2.54 (221)	0.10 ± 2.44 (221)
50 – 59 years	14.5 ± 2.51 (184)	14.5 ± 2.66 (184)	–0.23 ± 2.36 (182)	–0.21 ± 2.51 (182)
60 – 69 years	15.4 ± 3.20 (164)	15.4 ± 2.86 (165)	0.22 ± 2.98 (162)	0.27 ± 2.63 (163)
70 – 79 years	15.9 ± 3.24 (92)	15.8 ± 2.83 (91)	0.28 ± 3.03 (92)	0.20 ± 2.66 (91)
80 – 89 years	[illegible] ± 2.26 (25)	15.4 ± 2.33 (25)	–0.67 ± 2.20 (24)	–0.31 ± 2.43 (21)
90 – 99 years	14.0 ± 0.00 (2)	14.0 ± 1.41 (2)	–2.80 ± 0.11 (2)	–2.80 ± 1.56 (2)
Not treated with diuretics	14.2 ± 2.60 (1[illegible]61)	14.3 ± 2.53 (1558)	–0.03 ± 2.45 (1551)	0.05 ± 2.38 (1549)
Treated with diuretics	15.8 ± 2.67 (60)	15.8 ± 2.60 (60)	0.09 ± 2.40 (60)	0.07 ± 2.40 (60)
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Females	14.6 ± 2.67 (824)	14.7 ± 2.57 (823)	0.02 ± 2.47 (818)	0.08 ± 2.39 (817)
Total	14.3 ± 2.62 (1621)	14.1 ± 2.54 (1618)	–0.03 ± 2.45 (1611)	0.05 ± 2.38 (1609)

* Residual pressure = Difference between measured IOP and expected IOP the expected IOI being derived from a modified multiple regression equation

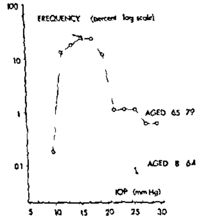


Fig 5

Relative frequency distribution of applanation pressures in two age groups

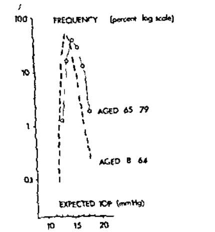


Fig 6

Relative frequency distribution of expected *pressures (for explanation see* text) in two age groups

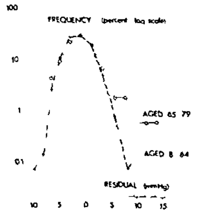


Fig 7

Relati e frequency di tribution of re sidual pres ures (for explanation see text) in two age groups

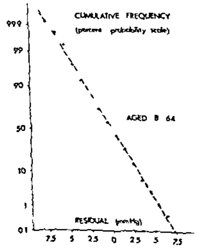


Fig 8

Plot on probability paper showing *that* the residuals are very nearly normally distributed up to 65 years

whole material might be given using the following slight modification of the regression equation

$$Y = 10.5 + 0.5\,X_1 + 0.15\,X_2 + 0.03\,X_3 - 0.1\,X_4 \quad \text{(cf. Table III)}$$

This expression was used to compute an "expected" pressure for each individual. The frequency distributions in two age groups are given in Fig. 6. The *correlation between "expected" and observed pressure was 0.36 in both eyes.*

The differences between measured and "expected" pressures – to be called "residual pressures" or "residuals" – were computed and found to be almost exactly normally distributed up to 65 years of age (Fig. 8). The hump in the frequency distribution of observed pressures in higher age groups (Fig. 5) remained after transformation into residual pressures (Fig. 7). The standard deviations were somewhat reduced in comparison with that of the uncorrected pressures (Table II). Plots of mean residuals against the independent variables (Figs. 9–12) demonstrated the effectiveness of the used procedure to eliminate linear effects. No further simple transformations of variables were suggested. The residual pressures were not affected by refraction (Fig. 13) or treatment with diuretics (Table II).

IV. Possible consequences of correction in practice

Residual pressures naturally correlated closely with observed pressure (r = *0.94 for both eyes). Nevertheless among persons not subject to antiglaucomatous* treatment in the present material from a statistical point of view 16 cases – all less than 50 years old – had "high" residual pressures combined with "normal" applanation readings. The residual pressures were normal in 19 cases with "high" applanation readings – all cases but one being more than 50 years old. Not more than 25 individuals – 14 less and 11 more than 50 years old – had values of both kinds of pressures between two and three standard deviations over the mean. Consequently the number of patients with *"borderline" pressures was doubled in younger and halved in older age groups* by the transformation of applanation pressures into residual pressures.

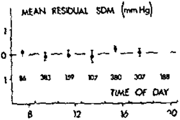


Fig 9

Change in mean residual pressure (for explanation see text ordinate) with independent variable (abscissa) The circles represent the mean the vertical lines one standard deviation of the mean above and below the mean and the numbers the number of observations in each class

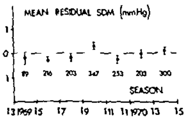


Fig 10
For legend see Fig 9
(Note that 1/3 means March 1st etc)

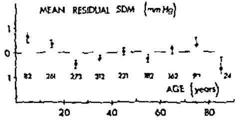


Fig 11
For legend see Fig 9

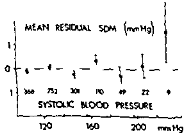


Fig 12
For legend see Fig 9

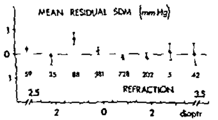


Fig 13
For legend see Fig 9

Discussion

The effects of age sex and time of day on the mean applanation pressure reported here are in all respects very similar to those found by Armaly (1962 1965 196) and by Graham & Hollows (1964) In several other studies smaller numbers of observations account for failures to secure statistical significance to the sex difference

Table III

Multiple regression analysis

Combined effects of sex season systolic blood pressure and time of day on average intraocular pressure

Variable		Mean ± std dev	Total correlation coefficient (r)	Partial regression coefficient (b)	Std dev of regr coeff	Significance
sex	(X_1)	1 5 ± 0 5 *	0 140	0 58	0 12	$p < 0\ 001$
season	(X_2)	3 5 ± 1 6 **	0 148	0 15	0 04	$p < 0\ 001$
systolic blood pressure	(X_3)	130 7 ± 21 5 mm Hg	0 287	0 030	0 003	$p < 0\ 001$
time of day	(X_4)	14 0 ± 3 7 hours	−0 174	−0 11	0 02	$p < 0\ 001$
age (not in equation)		37 8 ± 19 6 years	0 172	–	–	$p > 0\ 05$
average IOP	(Y)	14 3 ± 2 5 mm Hg				

y axis intercept (a) = 10 47

std error of estimate = 2 36 mm Hg

multiple correlation coefficient (R) = 0 364

Number of cases (n) = 1606

* sex/code male/1 female/2

** season/code July Aug /1 June Sept /2 May Oct./3 Apr Nov /4 March Dec./5 Jan Febr /6

factors (sex season time of day and systemic blood pressure) which to the best of our knowledge are not associated with glaucoma Obviously those factors should always be kept in mind when comparing the intraocular pressures in different populations There is a less evident but perhaps more important pos sibility that they should be taken into account when assigning prognostic signi ficance to tonometric measurements The more accurate method of correcting applanation pressures by transforming them into residuals which was used in this report is hardly practical It might be feasible however to lower the accepted normal limit 1 mm Hg summer afternoons to raise it by the same amount winter mornings and to measure the systemic blood pressure in pa tients with applanation readings over the limit – deducting 1 mm Hg from the intraocular pressure for every 30th mm Hg rise in blood pressure over a stated norm of say 150 mm Hg According to my observations a considerable number of patients who need help for a systemic rather than ocular hyper tension would be revealed in this way Long experience is needed to answer the question whether such a practice would improve the efficiency of routine tonometry and glaucoma screening

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Seasonal variations in the intraocular pressure with the highest level in January February and the lowest in July August were recently reported from Israel (Blumenthal et al 1970) The present study confirms the existence of an annual rhythm which however, seems to be somewhat less pronounced in Sweden with its more temperate climate

The dependence of the intraocular pressure upon the height of the systemic blood pressure has been considered to be slight and of little clinical significance apart from acute transient alterations (Duke Elder 1968) This opinion was however based on investigations with Schiötz tonometer (Akagi 1957) and according to unpublished data from our survey the effect of the systemic blood pressure on the intraocular pressure was less impressive with the Schiotz tonometer than with the applanation tonometer A discrepancy between the two methods could be explained assuming that not only the ocular tension but also the amount of choroidal blood available for expulsion by the tonometer is affected by the systemic blood pressure (Ytteborg 1960)

It has been commonly believed that the small hypermetropic eye is associated with a raised ocular tension but in the last few years several authors using the applanation tonometer have reported that a slightly increased pressure accompanies myopia rather than hypermetropia (Wallace & Lowell 1969 *Abdalla & Hamdi 1970 Tomlinson & Philips 1970) As stated earlier* no such effects were seen in the present material when the influences of blood pressure sex season and time of day were allowed for

Similarly the over all rise in ocular tension with age was shown by the multiple regression analysis to be dependent on a concomitant rise in systemic blood pressure The change with age from a normal distribution to one with an over representation of very high values was however not greatly affected by *the transformation of applanation readings into residuals Consequently* the relative frequency of persons with abnormally high pressure was increased between 65 and 79 years even after correction In this context it should be recalled that Stromberg (1962) concluded that the more severe forms of ocular hypertension usually develop during the years between 60 and 70

A definite increase in the prevalence of simple glaucoma with age is evident but there are no studies large enough to permit an assessment of the influence of the other pertinent factors on the prevalence of simple glaucoma There seems to be no significant sex difference (Hollows & Graham 1966) The general opinion is that a high blood pressure is prognostically favourable with regard to the visual field defects (François & Neetens 1970) and systemic hypertension is not found more frequently in patients with glaucoma than in controls of the same age and sex (Sunde 1951)

It can be concluded then that the intraocular pressure is affected by four

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NOTES ON THE STATISTICAL TREATMENT OF THE VISUAL RESOLUTION

BY

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The usual visual acuity scales are not interval scales they are not isomorphic to the numerical system known as arithmetic It is not permissible to manipulate the scores by adding and dividing which are necessary operations in finding mean variance and standard deviation The resulting statistical difficulties are discussed and some methods of calculation are presented It would however be preferable if the measurements could be performed with a chart graduated in equal steps in terms of minimum separabile
The *normal* distribution is discussed in its application to visual resolution. The relations between the visual resolution and some other variables are discussed

Key words visual acuity – interval scale – arithmetic mean – normal distribution – minimum separabile – ordinal scale – standard deviation

The fundamental basis of visual acuity is the minimum separabile or the minimum angle of resolution It is customary to define visual acuity as the reciprocal of the minimum separabile measured in minutes of angle

This is the definition of the Monoyer or decimal notation The Snellen nota

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The ordinal scale reflects only one of the characteristics of the real number series that of order The relations between the observations in an ordinal scale may be designated by the carat (>) The ordinal scale is unique up to a monotonic transformation as any order preserving transformation does not change the information contained in the ordinal scale The properties of an ordinal scale are *not* isomorphic to the numerical system known as arithmetic It is not permissible to manipulate the scores of an ordinal scale by adding or dividing which are necessary operations in finding mean and standard deviation

The interval or equidistant scale has the characteristics of an ordinal scale and in addition the distances between any two numbers on the scale are of known size An interval scale is characterized by a common and constant unit of measurement which assigns a number to each observation Any change in the numbers associated with the observations measured in an interval scale must preserve not only the order but also the relative differences of the observations That is the interval scale is unique up to a linear transformation $f(x) = cx + b$

Any non linear transformation e g $f(x) = 1/x$ or $f(x) = \log x$ will change the information yielded by the scale If the non linear transformation preserves the order of the observations the result will be an ordinal scale

The interval scale is a truly quantitative scale and all the common statistics (mean standard deviation Pearson correlation coefficient) are applicable

The scale of minimum separabile is one of equal steps or differences an interval scale in the visual acuity scale the intervals are drastically *unequal* The scale of visual acuity is an ordinal scale If the scale is ordinal there are some restrictions in the choice of statistical tests With ordinal scales the mode or the median can be used to measure the central tendency The most common and most sensitive of all measures of the central tendency the arithmetic mean *can* be used only with interval scales The range and the interquartile range can be used as measures of variability Use of variance and standard deviation is restricted to interval scales To study correlation use the different kinds of rank correlation coefficients The well known product moment correlation coefficient can be used only with interval scales

There are a great number of quantities which cannot be measured by interval scales and in such cases ordinal scales are very useful But if a quantity can be measured by an interval scale it is very unusual and exceedingly inefficient to present the measurements in an ordinal scale Such a practice results in a great loss of information

The Monoyer or decimal scale of notation is perilous because the steps are seemingly equal This danger was already known to Snellen who stated that

tion is defined by the equation V = d/D where d is the test distance and D is the distance at which the just discriminated details would subtend 1 minute of arc As the minimum separabile is equal to D/d the Snellen notation differs only formally from Monoyer s

If V is the visual acuity and **a** is the minimum separabile the definition gives the equation

$$V = \frac{1}{a} \tag{1}$$

The graphical representation of this equation as in Fig 1 of course results in a hyperbola It is easy to see from the diagram that equal changes of **a** correspond to very unequal changes of V If **a** increases from 1 to 2 V changes from 1 0 to 0 5 but a change of **a** from 9 to 10 will give a decrease of V from 0 11 to 0 10

Measurement (Stevens 1946 Siegel 1956 Torgerson 1960) is the assignment of numerals to observations in such a way that the numbers are amenable to analysis by operations according to certain rules The operations allowable on a given set of scores are dependent on the level of measurement achieved In the theory of measurement four levels of scales are usually discussed nominal ordinal interval and ratio Here we will limit the discussion to ordinal scales and interval scales

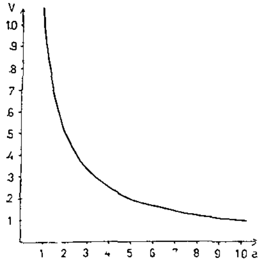


Fig 1

The relation between the minimum separabile (**a**) and the visual acuity (V) It is seen that equal changes of **a** correspond to very unequal changes of V

$$M_V = \frac{n}{\Sigma\left(\frac{1}{V}\right)} \tag{4}$$

$$\sigma_V = \frac{n}{\Sigma\left(\frac{1}{V} - \frac{1}{M_V}\right)^2} \tag{5}$$

ere M_V and σ_V are the mean and the standard deviation of visual acuity ;s is the method used by some authors who have chosen the denominators of ;llen fractions as their measure of visual resolution Those denominators are course proportional to the minimum separable

Here the mathematical treatment is based upon the interval scale of mini im separable but the result will be influenced by the very unequal steps of ;asurement of the usual visual acuity charts The visual acuity chart divides : data into classes with unequal class intervals The usual practice when a equency distribution is divided into classes is to treat all the values assigned any one class as if they were equal to the mid value of the class interval he values 1/V of eq (4) and (5) however give limits of class intervals not idvalues of classes This might not cause serious error if the class intervals ere equal and small but here the error will be difficult to estimate and pos bly rather large The class intervals and mid values for the Monoyer chart nd the Snellen 6 m chart are shown in Table 1

The substitution of the midvalues of classes for 1/V in eq (4) and (5) will nprove the results but the large class intervals in one end of the scale of leasurement are still an important source of error The distribution of the alues within the classes is unknown and the mean of those values within large class interval can differ much from the midvalue of that class

The variance and the standard deviation are valuable primarily to study the :rrors of measurement The unequal steps of measurement will make the errors much larger in one end of the scale than in the other This greatly reduces the usefulness of average values like the variance

Most of the difficulties and problems discussed above are caused by the non linear relationship between the minimum separabile and the visual acuity An obvious way of turning this relationship into a linear one is by logarithmic transformation The equation

$$\log V = 1 - \log a \tag{6}$$

is represented graphically by a straight line

The practical application of this principle results in visual acuity charts with

the fractions d/D should not be reduced to decimals because the decimal notation leads to erroneous conclusions

It sometimes happens that the decimal notation of visual acuity is treated statistically as if it were an interval scale

It might therefore be interesting to study theoretically some of the results of such an incorrect practice $1/n\ \Sigma\,(V)$ where n is the number of determinations will not give the arithmetic mean visual acuity If the expression is written $1/n\ \Sigma\,(1/a)$ it is evident that it gives the reciprocal of the harmonic mean of the minimum separabile The harmonic mean of a series of quantities is the reciprocal of the arithmetic mean of its reciprocals it is not a good measure of the central tendency and it is seldom used in modern statistics The harmonic mean of a series of quantities is always lower than the arithmetic mean the amount of difference depending largely on the magnitude of the dispersion relative to the magnitude of the mean

It has been shown (Scheibner 1873) that if the dispersion is small compared to the mean we have approximately the relation

$$H_v \approx M_v\ (1 - \frac{\sigma_v^2}{M_a}) \qquad (2)$$

where H_v and M_v and σ_v^2 are respectively the harmonic mean the arithmetic mean and the variance of the minimum separabile,
and consequently

$$\frac{1}{n}\Sigma\,(V) \approx \frac{1}{M_v\,(1 - \frac{\sigma_v}{M_v^2})} \qquad (3)$$

which value is always higher than the true value of the arithmetic mean visual acuity

To demonstrate the results of an attempt to calculate the variance of the visual acuities in the same way is quite feasible but it would involve some elaborate and space consuming algebra and seems unnecessary A short discussion is sufficient The variance is the mean square deviation from the arithmetic mean The mean square deviation from every other value also from $1/H_a$ is higher than the variance

Consequently attempts to calculate the arithmetic mean the variance and the standard deviation directly from the visual acuities results in values that are too high

A better way to treat visual resolution statistically involves the use of the minimum separabile that is the reciprocal of the visual acuity

$$M_V = \frac{n}{\Sigma\left(\frac{1}{V}\right)} \tag{4}$$

$$\sigma_V = \frac{n}{\Sigma\left(\frac{1}{V} - \frac{1}{M_V}\right)} \tag{5}$$

where M_V and σ_V are the mean and the standard deviation of visual acuity This is the method used by some authors who have chosen the denominators of Snellen fractions as their measure of visual resolution Those denominators are of course proportional to the minimum separabile

Here the mathematical treatment is based upon the interval scale of minimum separabile but the result will be influenced by the very unequal steps of measurement of the usual visual acuity charts The visual acuity chart divides the data into classes with unequal class intervals The usual practice when a frequency distribution is divided into classes is to treat all the values assigned to any one class as if they were equal to the mid value of the class interval The values 1/V of eq (4) and (5) however give limits of class intervals not midvalues of classes This might not cause serious error if the class intervals were equal and small but here the error will be difficult to estimate and possibly rather large The class intervals and mid values for the Monoyer chart and the Snellen 6 m chart are shown in Table 1

The substitution of the midvalues of classes for 1/V in eq (4) and (5) will improve the results but the large class intervals in one end of the scale of measurement are still an important source of error The distribution of the values within the classes is unknown and the mean of those values within a large class interval can differ much from the midvalue of that class

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Table 1

Monoyer chart			Snellen 6 m chart		
Visual acuity	Minimum separabile minutes		Visual acuity	Minimum separabile minutes	
	Class interval	Midvalue of class		Class interval	Midvalue of class
0.1	5.01–10.00	7.51	6/60	6.01–10.00	8.01
0.2	3.34– 5.00	4.17	6/36	4.01– 6.00	5.01
0.3	2.51– 3.33	2.92	6/24	3.01– 4.00	3.51
0.4	2.01– 2.50	2.26	6/18	2.01– 3.00	2.51
0.5	1.67– 2.00	1.84	6/12	1.51– 2.00	1.76
0.6	1.43– 1.66	1.55			
0.7	1.26– 1.42	1.34	6/9	1.01– 1.50	1.26
0.8	1.12– 1.25	1.19			
0.9	1.01– 1.11	1.06			
1.0	– 1.00	–	6/6	– 1.00	–

geometric gradation of letter sizes. This was first proposed by Green (1868). Different modifications of visual acuity charts with geometric gradations have been proposed by a great number of authors: Javal (1878), Nicati (1894), Sulzer (1899), Blaskovics (1923), Sloan (1959), the scale of Tscherning (Edmund & Moller 1925) and the Ago scale (1948).

The relation between log V and log **a** is linear.

A linear transformation will not change the information contained in an interval scale. If the scale of log **a** is an interval scale, the steps of visual acuity charts with geometric gradation are equal.

Is it probable that the log **a** scale is an interval scale? The condition for this is that the increase in size of stimulus required to produce a just noticeable increase in discrimination is a constant fraction of the initial size of stimulus. This is Weber's law, which has been shown to hold approximately for some sensory discriminations, but there is no evidence that it holds for the minimum separabile.

The geometric gradation of visual acuity charts is not theoretically satisfactory, but it is better than that of the usual charts. Although the steps in the scale of measurement are not equal, the inequality is less drastic. The value $1/n\ \Sigma\,(\log V)$ will give the logarithm of the geometric mean, which, although

not as good a measure of the central tendency as the arithmetic mean is better than the harmonic mean

The only interval scale for the measurement of the visual resolution is that of the minimum separabile If statistical treatment of the data is intended the best results will be achieved if the original measurements have been performed with a chart graduated in equal steps of minimum separabile Barány (1946a) has discussed how the measurement is influenced by the number of test letters in each row The ideal chart should contain the same number of test letters for each step of the scale which will result in a chart with a relatively large number of big test letters Such a chart will be rather unwieldy and it may be necessary to find some compromise

In statistical work it is very useful if the distribution of the variable under investigation is normal Physiologically the fineness of the retinal mosaic gives an upper limit to the visual resolution in such a case it is improbable that this is normally distributed The clinician studying eyes of people whose vision is reduced by disease however may often find samples with hump shaped curves of distribution which approximate the *normal distribution* The shape of the sample s curve of distribution should however be ascertained before the choice of statistical test is made An easy and usual way of doing this is to plot the values on probability paper If the distribution of the values is normal this will give a straight line If the range of measurements is small however this method has a source of error which does not seem to be well known

If one of the variables a log a and V is normally distributed the distributions of the two others are skew In Fig 2 it has been assumed that the variable log a is normally distributed and is consequently represented by a straight line The corresponding curves for the variables V and a have been calculated from the values of log a Diagrams drawn on the assumption that a or V is normally distributed give corresponding results It is seen from the curves for the variables V and a in Fig 2 that if the range of measurements is small a straight line will sometimes give a reasonably good fit This can be illustrated by a couple of examples

Lythgoe (1939) has published data which give the percentages of correct answers in the resolution of the gap in a series of Landolt rings of increasing sizes Barany (1946a) and Ogle (1953) have observed that if log a from Lythgoe s data is plotted on probability paper straight lines are formed However if Lythgoe s values are replotted with a or V on the abscissa instead of log a straight lines will fit the points nearly as well

White et al (1929) using a similar method to study the vision of some postal workers plotted visual acuities against percentages on probability paper

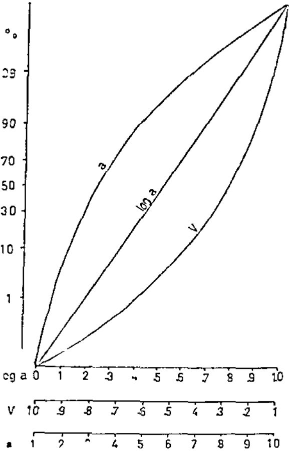


Fig 2

The distributions of the logarithm of the minimal separabile (log **a**) the minimum separabile (**a**) and the visual acuity (V) plotted on probability paper It is assumed that log **a** is normally distributed and consequently represented by a straight line. The corresponding curves for the variables **a** and V have been calculated from the values of log **a** It is seen from the curves for the variables **a** and V that if the range of measurement is small a straight line will sometimes give a good fit

and found that a *straight line fitted their values On replotting it is found that* values of **a** and log **a** will also result in straight lines

A non linear transformation of the scale of measurement will change the shape of the curve of distribution It might seem attractive to change in this way a skew distribution to one which is approximately normal Such operations are of course not very useful There are a number of statistical tests which require that the curve of distribution is normal but another condition for all *those tests is that* the scale of measurement is one of equal intervals so that it is possible to use the operations of arithmetic on the scores

The measurement of the visual resolution is not necessarily an end in itself. *It might be a means to* perform a derived measurement of some other variable which has a known relationship to the visual resolution.

If the visual resolution is regarded as a function of some independent variable, e.g. illumination, refraction, opacity of the media or radius of central scotoma, it might sometimes be possible to find a scale of measurement of the visual resolution which would make the relation linear. As the information yielded by an interval scale is not affected by a linear transformation, such a scale is one of equal intervals for the measurement of the independent variable. This is a principle which can be important if direct measurement of the independent variable is difficult or impossible.

As to illumination it has been found (Konig 1897, Lythgoe 1923) that there is a linear relationship between the logarithm of the intensity of illumination and V in the region from 0.015 to 65 millilamberts. The practical importance of this is reduced, however, by the fact that the intensity of illumination is easily measured directly, while the theoretical interest is reduced by the observation (Hecht 1925) that the seemingly linear part *might be the middle part* of a probability integral curve.

Snell & Sterling (1925) have investigated experimentally the relation between vision and opacity of the media. They used a series of diffusing filters which were made by cutting a fine mesh of thin lines into the surface of the glass. Several glasses were selected and standardized, *each of which reduced* the Snellen acuity *from* 20/20 *to* 20/40. When one to six such identical glasses were superimposed, a linear relationship was found between the number of meshed glasses and the log *a*. If it is assumed that the meshed glasses closely simulate the effect on visual resolution of an opacity of the cornea or the lens, the logarithm of the minimum separabile is a good measure of such an opacity.

The uncorrected visual acuity is in some countries an important *basis for military classification. This has resulted in* a number of publications on the relation between refraction and visual resolution. All measurements of visual acuity were made with Snellen charts, as was natural in view of the practical purpose of the investigations. The unequal steps in terms of minimum separabile of the Snellen chart, however, reduces the precision of measurement in cases of high ametropia.

Sloan (1951) using the data of Kempf et al. (1928) and Crawford et al. (1945) *found a linear* relationship between *a* and the spherical ametropia. The data of Hirsch (1945) and Eggers (1945) when replotted also give an approximately linear relationship between the myopia in diopters and the minimum separabile.

The radius of central scotoma is connected with the visual resolution in the

periphery Weymouth (1958) observed a linear relationship between the eccentricity of fixation in degrees and the minimum separabile The data of Wertheim (1894) Ludvigh (1941) and Randall et al (1966) confirm this observation at least for eccentricities below 30°

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HYPHAEMA FROM MICROHAEMANGIOMAS

BY

ANDERS SELLMAN

Spontaneous bleeding into the anterior chamber of the eye because of neovascularisation of the iris is uncommon Known causes are diabetes post thrombotic changes vasculitis glaucoma and various tumours of the eye An until 1968 unknown type of neovascularisation with micro haemangiomas has been described Spontaneous bleeding from vessels of this kind in one patient was reported in 1969 After finding one case with spontaneous hyphaema because of microhaemangiomas the author examined a large population regarding neovascularisation of the iris Another two cases were found one with spontaneous hyphaema The two cases with hyphaema are described and discussed

Key words bleeding – haemangioma – hyphaema – microhaemangioma – neovascularisation – eye

Only a few cases of spontaneous bleeding of the anterior chamber are on rec ord The predominant type of haemorrhage is that seen in diabetic neovascu larisation of the iris Other known causes of bleeding in the iris are non diabe tic neovascularisation (post thrombotic changes vasculitis glaucoma and iritis) vascularising tumours of the iris lymphosarcoma papillary cystadenoma ju venile xanthogranuloma and capillary fragility because of C avitaminosis

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vascularised fragments of pupillary membrane (Rydberg 1964) and a type of vascularisation with very small microhaemangiomas* in the pupillary margin reported in recent years Cobb et al (1968 1970) in England found more than 100 cases with this lesion Rosen & Lyons (1969) described a patient with spontaneous hyphaema from microhaemangiomas in the pupillary margin Riffenburgh (1965) reported a case with recurrent bleeding from the surface of the iris but he did not mention microhaemangiomas

This paper reports two cases with spontaneous hyphaema from microhaemangiomas in the pupillary margin

Case No 1 A. B C -23

The patient a 45 year old woman had on various occasions consulted the Eye Clinic in Halmstad because of impaired vision of the left eye But by the time of the examinations the symptom had disappeared and no satisfactory explanation could be offered Ocular hypertension was diagnosed on one occasion but the tension curve was normal as was the result of the provocation test. On another occasion corpuscular aqueous flare suggested iritis The patient was requested to report at the clinic as soon as she noticed any impairment of vision She did so and at examination a small hyphaema was seen as well as blood in the aqueous The blood originated from a very small vascular tuft at the 6 o clock position in the pupillary margin. The margin also showed several vascular tufts or microchaemangiomas (Fig 1) Corresponding changes were found in the other eye Examination with the slit lamp (X 25) showed the angiomas to be very small and somewhat oval and the protruding vascular tuft to be embedded in an almost transparent supporting substance The haemangiomas were situated in a well developed pupillary margin No angioma could be seen on the surface of the iris In

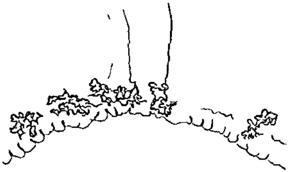


Fig 1

The upper pupillary border of the left eye Five radiating vessels can be seen In the pupillary border there are contorted vessels which *cohere to tufts*

(Drawn from a Kodachrome transparency)

From the Department of Ophthalmology in Malmo
(Head Professor Gote Österlind)
and the Eye Clinic County Hospital Halmstad
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tonic dystrophy In nine of these patients Cobb also found cataract of varying severity But the severity did not appear to vary with the presence of micro haemangiomas

Riffenburgh s (1965) and Rosen s (1969) patients like ours showed no signs of systemic disease

Analysis of Cobb s Rosen s and the present material showed that micro haemangiomas occur almost only in persons above 45–50 years This may be because angiomas appear late and are manifestations of true neovascularisa tion The patients used in this investigation however had an average age of 50 8 years (excluding children below 9 years) since most of them had con sulted the clinic because of presbyopia and other changes due to age

It is too early to decide whether hyphaema is a common complication of microangiomas but demonstration of three cases of haemorrhage among some what more than 100 patients with known microhaemangiomas suggests that the complication is not rare

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the irides superficial vessels extended radially towards the pupillary margin apparently supplying at least part of the angioma The hyphaema was absorbed within 1³ hours

Besides this the investigation showed nothing remarkable the blood pressure was normal as were the heart and lungs The blood sugar blood coagulation time, and the result of the capillary fragility test according to Owren were normal and the urine contained no blood corpuscles Neither the patient s history nor laboratory studies suggested any underlying systemic disease The patient has since been followed up for 1½ years During this period the angiomas have decreased slightly in size and no new bleeding episode has occurred

Case No 2. I J -94

The patient a 76-year old woman consulted the Eye Department in Malmo because of a spot in the right eye which had occurred a few hours before the examination. Vision had become temporarily impaired The patient s vision was otherwise normal The eye had not been painful At examination she had a hyphaema in the right eye A blood clot was situated in the lower part of the anterior chamber and tapered towards a vascular tuft in the 6 o clock position of the pupillary margin There was no bleeding at time of examination. The pupillary margin of the right eye contained 7 and that of the left eye 9 vascular tufts or microhaemangiomas Several of the angiomas were situated close to one another and were connected by blood vessels The angiomas were broader and contained more vascular tufts than in case 1 The iris of the right eye showed a superficial vessel running almost concentrically with the pupillary margin. At the examination she had resting dyspnoea and complained about diffuse cardiac symptoms She denied diabetes She had been examined at the Eye Clinic in 1953 and her records contained no remarks on angiomas The clot disappeared after three days The patient was requested to return for re examination but declined

Discussion

Since 1968 when case 1 was discovered some 2 000 patients have been examined for microhaemangiomas of the pupillary margin The examinations were carried out by careful examination with the slit lamp (× 25) In this unselected series of patients two further cases of microhaemangiomas of the pupillary margin were discovered and one of them (case 2) also had a haemorrhage in the anterior chamber

The frequency of microhaemangiomas of the pupillary margin in this series was low In an English 9 month series (Cobb 1968) 44 of an unspecified number of patients were found with this change but without any hyphaema In certain disease groups the frequency of microhaemangiomas seems to be higher Thus Cobb et al (1970) found haemangiomas in five out of ten cases of myo

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ruption of blood flow The studies of Seitz (1964) in particular are quoted to support this pathogenesis since this author could not find any obstructing thrombi in the retinal vessels of patients who had the clinical picture of retinal vein occlusion and died from other diseases It is known however that the wall of the central retinal vein has a strong fibrinolytic capacity (Pandolfi 1967) and that thrombi are often found to be friable under necroscopy and are easily dislodged during preparation of the specimens (Mustard et al 1964) The frequent lack of demonstrable thrombi can therefore not exclude thrombosis as an essential factor in the pathogenesis of retinal venous occlusion

In the last few years much effort has been devoted to the search for coagulation and fibrinolytic changes possibly capable of facilitating the occurrence of thrombosis A pioneer study in this field has been conducted by Nilsson et al (1961) They described a patient who had an abnormally large amount of an inhibitor of fibrinolysis and consequent severely impaired fibrinolytic activity which resulted in death from recurrent widespread thrombosis They called this state morbus thromboticus Other patients with thrombosis and increased inhibitors of fibrinolysis including one with bilateral occlusion of retinal veins (Pandolfi 1970) have since been reported

Very recently Isacson & Nilsson (1971) in a study of 117 cases of idiopathic venous thrombosis of different parts of the body could show that a high percentage (55 %) of these patients had an abnormally low content of fibrinolytic activators in the walls of their superficial veins As many as 38 % of these patients also had defective mobilization of endogenous fibrinolytic agents as witnessed by an abnormally low fibrinolytic response to standardized stimuli such as venous occlusion

This paper reports an investigation of coagulation and fibrinolytic systems in 23 patients with occlusion of the retinal vessels

Material and Methods

Clinical material The study included 23 patients with thrombosis of retinal vessels referred to this laboratory from different eye clinics in Sweden in the period 1966–1970 The material divided according to the vessel involved is reported in Table I It includes one previously described case (Pandolfi 1970)

Laboratory methods As a rule the following determinations were made platelet count (Bjorkman 1959) platelet adhesiveness according to the whole blood method of Hellem (1960) as *modified* by Cronberg et al (1966) whole blood clotting time in glass tubes (Nilsson et al 1961) prothrombin + procon

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COAGULATION AND FIBRINOLYTIC STUDIES IN 23 PATIENTS WITH OCCLUSION OF THE RETINAL VESSELS

BY

MAURIZIO PANDOLFI SUNE ISACSON and BIRGER ASTEDT

The authors report the results of coagulation and fibrinolytic analysis in 23 patients with occlusion of the retinal vessels 13 of these patients showed pathological changes such as increased platelet adhesiveness factor V factor VIII inhibitors of urokinase and plasmin or decreased fibrinolytic activity of the venous walls It is suggested that these changes play a role in the occurrence of thrombosis These results would seem to indicate that coagulation and fibrinolytic analysis should be made in patients with retinal occlusion

Key words retina – thrombosis of central vein – blood – coagulation – fibrinolysis

Recent studies (Rabinowicz et al 1968 Seitz 1964) have revived the hypothesis propounded by Verehoff (1907) and Scheerer (1923) that so called thrombosis of the retinal veins are caused not by a thrombus but by degenerative changes of the vascular wall leading to stenosis of the lumen and inter

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the liquid was coagulated with 0 01 ml (Topostasin® 20 NIH/U/ml) The mix ture was spread over an area of about 10 cm of the slide resulting in a fabrin film about 10 µm thick Four slides were prepared for each specimen To allow the fibrin to stabilize the slides were placed horizontal for 30 min in a moist chamber at room temperature (21–24°C) They were afterwards placed in an other moist chamber at 37°C The slides of each series were incubated for 0 5 10 and 20 min respectively after which they were fixed in formalin and stained with Harris hematoxylin Three fairly distinct degrees of fibrin diges tion were recognized namely grade I microscopic punctate areas of lysis in most of the sections grade II gross lytic areas of irregular outline and some times confluent grade III dissolution of most or all the fibrin in contact with the sections A grade I slide was allotted 1 point a grade II slide 2 points and a grade III 3 points Degrees of digestion between grades 0 and I 1 and II and II and III were allotted 0 5 1 5 and 2 5 points respectively The total number of points scored by the set of four slides was taken as a measure of the fibrinolytic activity of the sample

Results

Of the 23 patients examined only one (case No 19) showed perfectly normal values for all the coagulation and fibrinolytic factors (Table II) No unequia cally pathological changes were found in 9 patients (Nos 1 5 7 13 14 16 21 22 23) the low P & P values of Nos 5 16 and 22 being ascribable to anti coagulant therapy Of the remaining 13 patients with pathological changes 2 (Nos 2 and 10) had increased platelet adhesiveness alone 2 (Nos 4 and 8) associated with high level of urokinase inhibitors and 1 (No 6) with decreased fibrinolytic activity of the walls of superfical veins In 1 patient (No 3) the only abnormality was an increased serum content of urokinase inhibitor Three patients (Nos 9 11 and 12) showed low fibrinolytic activity in the vein walls alone and 1 (No 15) also a high level of factor V Factor VIII was increased together with α macroglobulins in patient No 17 and together with fibrino gen in patient No 20 Finally factor V alone was increased in 1 patient (No 18) The clotting time thrombin time blood spontaneous fibrinolytic activity and the level of antiplasmin were invariably within normal ranges The resul of some coagulation and fibrinolytic analysis are reported in details in Figs 1 2 and 3

The examination of 6 cases (Nos 3 7 8 9 12 14) after periods varying from 2 months to 1 year showed no substantial changes In case No 3 increased

Table I
Cases studied

Number of patients	Occluded retinal vessel
17	Central vein in one eye
2	Central vein in one eye and vein branch in the other eye
3	Main vein branch(es) in one eye
1	Central artery

vertin + factor X (P & P) (Owren & Aas 1951) factor V (Wolf 1953) factor VIII (Nilsson et al 1957) fibrinogen (Nilsson & Olow 1962a) thrombin time (Niléhn & Nilsson 1964) fibrinolytic activity of plasma and resuspended euglobulin precipitate on fibrin plates (Nilsson & Olow 1962b) euglobulin clot lysis time (Nilsson & Olow 1962b) plasminogen (Nilsson et al 1957) inhibitors of plasminogen activation by urokinase (urokinase inhibitors) (Paraskevas et al 1962) A macroglobulin (Ganrot 1966) degradation products of fibrinogen and/or fibrin (FDP) (Nilehn 1967)

Local fibrinolytic activity during venous occlusion of the arms Venous occlusion was produced by placing a sphygmomanometer cuff around each upper arm and inflating it to a pressure midway between the systolic and diastolic blood pressure in the arm for 20 minutes (Robertson et al 1971) Blood samples for determination of the fibrinolytic activity were drawn before application of the cuff and immediately before the cuff was deflated The samples were collected from an antecubital vein The fibrinolytic activity of plasma and that of resuspended euglobulin precipitate were determined on unheated fibrin plates as previously described (Nilsson & Olow 1962b)

Plasminogen activator content in superficial veins A segment 0 5–1 0 cm long of the distal part of the cephalic vein or a superficial hand vein was excised under local anaesthesia (0 5 % Carbocain®) The veins were examined by the fibrinolysis autography technique of Todd (1959) modified by Pandolfi et al (1968) Frozen sections (6–8 μm) of the vein were cut on a cryostat microtome and covered with 0 06 ml of a mixture consisting of 1 05 ml of 1 % bovine fibrinogen (Kabi) 0 1 ml human plasminogen (Kabi grade A) dissolved in distilled water to a final concentration of 10 arbitrary caseinolytic units per ml (Hedner & Nilsson 1965) and 0 3 ml phosphate buffer Immediately afterwards

Table II cont

P & P	F V	F VIII	F.A vein	UK inhib	A M	Plasminogen
n	n	n	n	n	n	n
n	n	slightly decr	n	slightly incr	n	n
n	n	n	n	incr	n	slightly decr
n	n	slightly incr	n	incr	slightly decr	n
decr	n	n	n	n	n	n
n	n	n	decr	n	n	n
n	n	n	n	n	slightly incr	n
n	slightly decr	n	slightly decr	incr	n	n
n	n	n	decr	n	n	n
n	n	n	n	n	slightly decr	n
n	n	n	decr	slightly incr	n	n
n	n	n	decr	n	slightly incr	n
n	slightly decr	n	n	n	n	n
slightly incr	n	n	n	n	n	n
n	incr	n	decr	n	n	n
decr	n	n	slightly decr	n	n	n
n	n	incr	n	n	incr	n
n	incr	n	n	n	n	n
n	n	n	n	n	n	n
n	n	incr	n	n	n	n
n	n	n	n	n	n	n
d cr	n	n	n	n	n	n
n	n	n	n	n	[illegible]	[illegible]

Table II

Synopsis of the results (Platl adhesiv = platelet adhesiveness Fib = fibrinogen P & P = prothrombin proconvertin and factor X F V = factor V F VIII = factor VIII F A vein = fibrinolytic activity of the wall of superficial veins Uk inhib = inhibitors of urokinase A M = α_2 macroglobulins n = normal value)

Case	Sex	Age	Occluded retinal vessel	Examination interval (in months)	Platl adhesiv	Fib
1	M	52	Central vein R E	4	slightly incr	n
2	M	66	Central vein L E	11	high	n
3	M	53	Central vein L E and 2 main branches R E	3	slightly incr	n
4	F	48	Main vein branch R E	1	incr	n
5	F	67	Central vein R E	2	slightly incr	n
6	F	59	Central vein L E	1	incr	n
7	F	30	Central vein L E	1/	n	n
8	M	67	Central vein L E	1	incr	n
9	M	61	Central artery R E	1/	slightly incr	slightly incr
10	M	52	Central vein R E	1/2	incr	slightly incr
11	F	48	Central vein L E	2	slightly incr	n
12	M	35	Central vein R E	1	n	n
13	F	24	Central vein L E	1/	n	n
14	M	54	Central vein L E	1	n	n
15	M	52	Main vein branch R E	1/4	slightly incr	n
16	F	62	Central vein L E	4	n	n
17	F	63	Central vein L E	2	slightly incr	n
18	F	42	Central vein L E	1	slightly incr	n
19	F	76	Central vein L E	2	n	n
20	F	50	Central vein R E	14	n	incr
21	M	56	Central vein R E	1	n	slightly incr
22	M	44	Main vein branch L E	1 2	slightly incr	n
23	M	58	Central vein L E	3	n	slightly incr

Table II cont

P & P	F V	F VIII	F.A vein	UK inhib	A M	Plasminogen
n	n	n	n	n	n	n
n	n	slightly decr	n	slightly incr	n	n
n	n	n	n	incr	n	slightly decr
n	n	slightly incr	n	incr	slightly decr	n
decr	n	n	n	n	n	n
n	n	n	decr	n	n	n
n	n	n	n	n	slightly incr	n
n	slightly decr	n	slightly decr	incr	n	n
n	n	n	decr	n	n	n
n	n	n	n	n	slightly decr	n
n	n	n	decr	slightly incr	n	n
n	n	n	decr	n	slightly incr	n
n	slightly decr	n	n	n	n	n
slightly incr	n	n	n	n	n	n
n	incr	n	decr	n	n	n
decr	n	n	slightly decr	n	n	n
n	n	incr	n	n	incr	n
n	incr	n	n	n	n	n
n	n	n	n	n	n	n
n	n	incr	n	n	n	n
n	n	n	n	n	n	n
decr	n	n	n	n	n	n
n	n	n	n	n	n	n

platelet adhesiveness and inhibitors of urokinase were confirmed Case Nos. 8 9 and 12 showed again a decreased content of plasminogen activator in the superficial vein Re examination repeated the results of an essentially normal coagulation state of case No 7 A slightly increased P & P-level was again obtained in case No 14

Discussion

The results show that most of the patients with occlusion of the retinal vessels had changes of the coagulation and fibrinolytic systems which were apt to more prone to clot as the increased platelet adhesiveness and the increased levels of factor VIII and factor V or they implar the mechanism of fibrin dissolution as the low fibrinolytic activity of the vessel walls and the increased serum content of urokinase inhibitors It is remarkable also that the slight changes observed in these patients have almost exclusively the effect of displacing the hemostatic balance i e the equilibrium assumed to exist in the living organism between coagulation and fibrinolysis (Astrup 1956) toward fibrin formation

Re examination of some of the patients generally confirmed previous results thereby suggesting that the changes observed were a lasting condition

These results may warrant pathogenetic and clinical consideration The

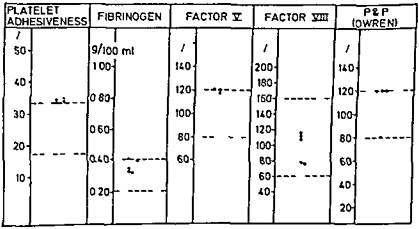


Fig 1

Coagulation analysis in patients with retinal vascular occlusion Each dot denotes 1 patient Areas between broken lines denote normal range

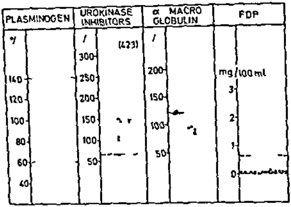


Fig 9
Fibrinolytic analys s in patients with retinal vascular occlusion Each dot denotes 1 patient Areas between broken lines denote normal range

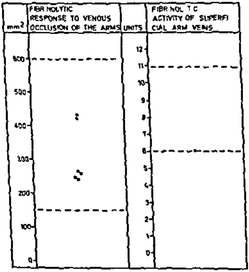


Fig 3
Local fibrinolytic activity in the blood during *venous occlusion* of the arms expressed in mm² of lysis produced by resuspended euglobulin precipitate on fibrin plates (*left*) and plasminogen activator content determined histochemically *in* arbitrary units in the distal part of the cephalic ve n (*right*) in patients with *retinal vascular* occlusion. Each dot denotes 1 patient Areas between broken lines denote normal ranges

finding in the majority of the cases of clear coagulation and fibrinolytic changes predisposing to thrombosis suggests that systematic changes concur with the already known vascular alterations in determining the retinal occlusion In the choice of therapy it would therefore appear wise to examine patients with retinal occlusion for disorders of the coagulation and fibrinolytic system Administration of exogenous fibrinolytic agents such as streptokinase and of anticoagulants seems to be especially indicated in cases of retinal occlusions accompanied by impairment of the fibrinolytic system As mentioned such changes have been shown often to coexist with venous thrombosis of various districts (Isacson 1971) Interestingly recent research has demonstrated that fibrinolysis can be durably enhanced by oral administration of phenformin and ethyloestrenol (Isacson 1971) This association enhances fibrinolysis by increasing the fibrinolytic activity in the vessel wall as witnessed by histochemical investigation (Isacson 1971) Long term treatment with these substances is at present being carried out on trial at our laboratory on patients with thrombosis of various districts including the eye Unfortunately no substance has yet been found to correct a high level of fibrinolytic inhibitors while the use of dextran infusion to decrease platelet adhesiveness (Cronberg et al 1966) is scarcely suited to clinical application Administration to corticosteroids which have recently been shown to depress fibrinolysis (Isacson 1971) should be avoided in these patients

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A CLINICAL STUDY OF THE CENTRAL AND PERIPHERAL THICKNESS AND CURVATURE OF THE HUMAN CORNEA

BY

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Measurements of corneal thickness and curvature were taken with a modified Haag Streit type 1 attachment and a Topographic Ophthalmo meter along the visual axis and at 25° temporal to this direction in the right eyes of 65 subjects aged 18 to 27 years (35 females and 30 males) A positive relationship was found between the central and peripheral cornea for both curvature and thickness No sex difference was apparent for either central or peripheral corneal thickness The peripheral corneal curvature was found to correlate significantly with the peripheral corneal thickness (a thick peripheral cornea being found in an eye with a flat peripheral curvature) although central corneal thickness was not found to be related to central corneal curvature These findings are considered in relation to a suggested form for the posterior corneal surface and in the aetiology of closed angle glaucoma

Key words corneal thickness – corneal curvature

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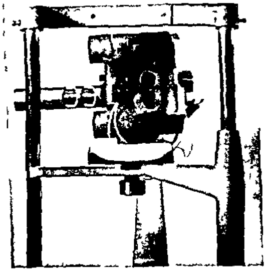


Fig 2

The Topographic Ophthalmometer designed by Bonnet to which is attached an extra fixation light to facilitate measuring the vertical curvature of the cornea at angle of 25° temporal to the visual axis of the right eye

thickness of the cornea to be taken at a point 25° to the temporal side of the visual axis of the right eye (Fig 1)

The segment scale of the attachment is calibrated with equal divisions although the relationship between the angle of rotation of the glass plates and corneal thickness is not a linear one This necessitates a correction factor being applied to the reading obtained dependent on the radius of the cornea at the point of measurement It was necessary therefore to measure the radius of curvature of the cornea both centrally and at an angle of 25° temporal to the visual axis In both cases the vertical radius was required as it was a vertical section of the cornea which was being considered

Central corneal curvature is measured in conventional ophthalmometry by the optical juxtaposition of the images of two mires which are formed by points on the cornea separated by up to 3 mm This is acceptable for the central region only as this area has a uniform curvature The same is *not* true however of the peripheral parts of the cornea Consequently measurements of the curvature of the periphery must use a small single mire which occupies only a small area of corneal surface (0 25 mm for the instrument in this survey) A device which is adaptable for use as a small mire kerato

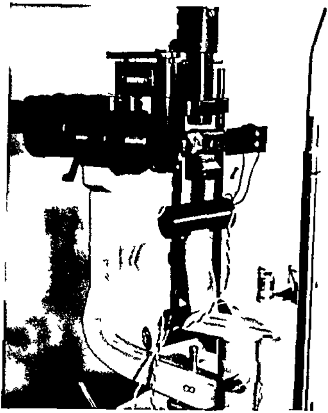


Fig 1
The *Haag Streit type 1* depth measuring attachment modified according to the suggestions of Mishima & Hedbys (1968) The extended diaphragm to which are attached two ophthalmoscope bulbs allows for measurement of peripheral corneal thickness

Measurement of corneal thickness with the Haag Streit depth measuring attachment type 1 involves determining the apparent thickness of the corneal optical section when the slit lamp beam passes through the tissue perpendicular to its surface The principle of this method was originally suggested by Juillerat & Koby (1928) and developed by Jaeger (1952) Mishima & Hedbys (1968) modified the device to allow for measurements of the thickness of the cornea at points away from its centre With this modification which is theoretically correct (Ehlers & Hansen 1971) the measurements of the thickness of the peripheral parts of the cornea can be made with good reproducibility (Mishima & Hedbys 1968)

In the study to be described a Haag Streit attachment was modified according to the suggestions of Mishima & *Hedbys (1968)* an *extra fixation light* mounted on the arm of the attachment allowed measurements of the peripheral

Table I

Rank correlation test applied to the inter relationship between central and peripheral corneal curvature and thickness

Dimensions	Correlation coefficient	Level of significance
Central corneal curvature and central corneal thickness	+ 0.187	$p < 0.[illegible]$
Central corneal curvature and difference in thickness centre and periphery	+ 0.044	$p < 0.[illegible]0$
Central corneal curvature and difference in curvature centre and periphery	+ 0.0[illegible]1	$p < 0.50$
Peripheral corneal curvature and central corneal curvature	+ 0.888	$p < 0.001$
Peripheral corneal curvature and peripheral corneal thickness	+ 0.3[illegible]8	$p < 0.01$
Peripheral corneal curvature and difference in thickness centre and periphery	+ 0.047	$p < 0.50$
Peripheral corneal thickness and central corneal thickness	+ 0.869	$p < 0.001$
Difference in curvature centre and periphery and difference in thickness centre and periphery	+ 0.073	$p < 0.50$
Difference in curvature centre and periphery and central corneal thickness	+ 0.[illegible]96	$p < 0.0[illegible]$
Difference in curvature centre and periphery and pheripheral corneal thickness	+ 0.3[illegible]9	$p < 0.01$

b) Central and peripheral corneal curvature

A correlation coefficient of + 0.888 was found for these two on the Rank correlation test which was significant at the 0.01 % level A cornea with a steep central curvature was found to be steeply curved at 25° to the temporal side A steep cornea was not found to flatten more or less rapidly in the periphery than a flat cornea (the correlation coefficient for central curvature against difference in central and peripheral curvatures was + 0.0[illegible]1)

meter is the Topographic Ophthalmometer designed by Bonnet (1964) It was used in this survey An extra fixation target was added to enable a reading of the vertical curvature of the cornea to be taken at 25° temporal to the visual axis (Fig 2)

The aims of the present study were to investigate

(a) the relationship between the central and peripheral corneal thickness

(b) he relationship between the central and peripheral corneal curvature.

(c) the relationship between the thickness of the cornea and its curvature both centrally and peripherally

(d) the effect of the sex of subjects within the same age groups on the thickness of the cornea

Material

This survey was conducted on 65 students of the University of Manchester Their ages were between 18 and 27 years 35 were female and 30 male None of the subjects had any history of corneal disease or of contact lens wear In each case measurements were taken only on the right eye

Method

Measurements of corneal thickness were taken (i) centrally (along the visual axis) and (ii) at 25° temporal to this direction with the modified Haag Streit type 1 depth measuring attachment described above The corneal thickness recorded was the mean of three readings in each case

Measurements of corneal curvature were then taken with the topographic ophthalmometer in the same position as the thickness measurements

Results

a) Central and peripheral corneal thickness

The relationship between these two was statistically analysed for the 65 subjects by the rank correlation method of Spearman A correlation coefficient (R) of + 0 869 which was significant at the 0 01 % level by the t test was found (see Table I) i e the greater the central thickness of the cornea the greater was the peripheral thickness

Table II

Mean and standard deviations of the corneal thicknesses (central and peripheral) found for three groups of subjects with corneal curvatures (central and peripheral) within specified limits Peripheral corneal thickness is found to increase with greater degrees of peripheral corneal flattening no significant relationship is found between central corneal thickness and curvature

	Central corneal curvatures (mm)		
	7 [illegible]0 to [illegible] 60 (mean = 7 46 ± 0 10[illegible])	7 61 to 7 85 (mean = 7 71 ± 0 045)	7 86 to 8 40 (mean = 7 96 ± 0 130)
Central corneal thickness (mm) (mean ± standard deviation)	0 547 ± 0 036	0 5[illegible]1 ± 0 039	0 559 ± 0 0[illegible]4

	Peripheral corneal curvatures (*mm*)		
	7 [illegible]5 to [illegible] 70 (mean = 7 54 ± 0 118)	7 71 to 8 00 (mean = 7 85 ± 0 060)	8 01 to 8 50 (mean = 8 12 ± 0 140)
Peripheral corneal thickness (mm) (mean ± standard deviation)	0 588 ± 0 0[illegible] 0	0 601 ± 0 0[illegible]8	0 624 ± 0 026

(R = + 0 044 p < 0 50) between peripheral corneal curvature and the difference in central and peripheral thickness (R = + 0 047 p < 0 50) and between the differences in curvature and thickness of the central and peripheral corneal regions (R = + 0 073 p < 0 50)

d) Sex and corneal thickness

The mean and standard deviations of the central and peripheral corneal thickness were found for the male and female samples within the age range 18 to [illegible] years (Table III) No significant differences were found for either the central or peripheral thickness between the samples on the t test (t = 0 292 p < 0 50 and t = 0 548 p < 0 50 respectively)

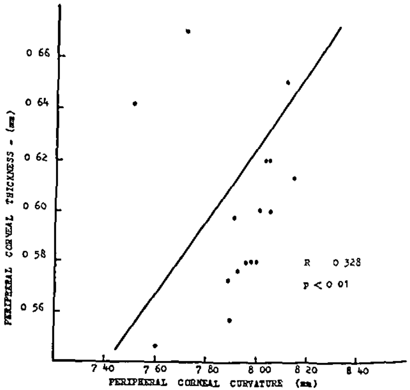


Fig 3

A scattergram with the regression line of values of corneal thickness on values of corneal curvature for measurements taken at an angle of 25° temporal to the visual axis

c) The thickness and curvature of cornea

The thickness of the central cornea was not found to be related to the radius of curvature of this region ($R = +0.187$ $p < 0.25$) The central corneal thickness was however significantly related to the difference in curvatures between the central and peripheral corneal regions ($R = +0.296$ $p < 0.02$) a thick cornea centrally being found in eyes with a large difference in curvature between these two regions

The *peripheral corneal curvature* was found to be significantly *related* to the *peripheral thickness* of the cornea ($R = +0.328$ $p < 0.01$) – see Fig 3 and Table II – a thick peripheral cornea being found in eyes with a flat peripheral curvature Peripheral corneal thickness was also positively related to the difference in curvatures between the centre and periphery ($R = +0.379$ $p < 0.01$)

Significant relationships were not found between central corneal curvature and the difference in thickness of the cornea at the centre and the periphery

error in the measurement of corneal thickness taken here would not invalidate the relationships found between curvature and thickness as the same observer recorded all measurements It is also probable that differences exist between samples even when readings are taken by the same observer on one instrument and possible that some intrinsic difference occurs between national populations (the results obtained here are compared with those from the U S A Australia and Denmark)

The measurements of peripheral corneal thickness with the Haag Streit at tachment are of the same order as those given by Mandell & Polse (1969) for an angle of 25° to the temporal side of the visual axis They also compare favourably with the results of Maurice & Giardini (1951) although these wor kers employed a different measuring device

Martola & Baum (1968) found that the peripheral corneal thickness had a tendency to decrease with age But as all the subjects in this study were within the same group (18 to 27 years) and as the age effect noted by Martola & Baum was confined to the group over 50 years of age it is unlikely to have affected these results

The finding of no relationship between central corneal thickness and cur vature and of no sex difference for central thickness confirms the observations of Hansen (1971)

The findings of this survey that a cornea which is thick or flat centrally also tends to be relatively thick or flat at the periphery are perhaps to be expected But the finding that a statistically significant relationship exists between peripheral corneal curvature and peripheral thickness is an interesting one i e a cornea which was found to be thick in the periphery tended to have a relatively flat peripheral curvature It is consistent with the three findings mentioned above to postulate a curvature for the *posterior* surface of the cornea which is fairly *constant* in all eyes The cornea with the thickest periphery would then be one in which a flat anterior central *and* peripheral curvature is combined with a large central thickness

The observations that a cornea which is thick in the periphery tends to be associated with a large difference in curvature between the centre and periphery probably reflects the positive relationship found between the dif ference in corneal curvature (centrally and peripherally) and central corneal thickness (Table I) A high correlation has been found between central and peripheral corneal thickness

The results of this survey are of interest in the aetiology of closed angle glaucoma A thick cornea at the periphery could be a predisposing factor to angle closure A study of the thickness and curvature of the peripheral cornea in closed angle glaucoma is planned

Table III

Mean and standard deviations of central and peripheral corneal thickness for the male, female and total samples

Sample	Central corneal thickness	Peripheral corneal thickness
Males	0 556 ± 0 022 mm	0 611 ± 0 037 mm
Females	0 549 ± 0 044 mm	0 599 ± 0 030 mm
Males and females	0 552 ± 0 039 mm	0 604 ± 0 039 mm

Discussion

Only one eye the right was measured throughout this survey as Hansen (1971) has shown that the central corneal thickness measured by the Haag Streit type 1 attachment is systematically greater in the left than in the right eye When measurements of central corneal thickness are taken along the visual axis of each eye the difference between the two eyes has been shown by Ehlers & Hansen (1971) to be due to the angle kappa (the angle between the line of sight and a line perpendicular to the anterior corneal surface and going through the centre of the pupil) Measurement of only one eye reduced the possibility of bias as a result of this factor

The values recorded for central corneal thickness (see Table III) are slightly larger than most of the previous determinations recorded in the literature This may be partly explained by the position of alignment of the two halves of the optical section during measurement In this survey the anterior surface of the epithelium of the lower section was aligned with the posterior surface of the endothelium of the upper section This technique was adopted as it was felt that this represented the full corneal thickness but it differs from that adopted by others who appear to align the whole of the epithelium with the whole of the endothelium (Mishima & Hedbys 1968) A factor contributing to the variations in measurements between workers is the use of different instruments and it is therefore possible to compare directly only results obtained with the same instrument (Hansen 1971) The measurements recorded in this study with the Haag Streit pachometer are still however slightly greater than those of Mishima & Hedbys (1968) Lowe (1969) and Hansen (1971) This may be attributable to an observer error similar to that found in keratometric determinations of corneal curvature (Brungardt 1969) Such an

error in the measurement of corneal thickness taken here would not invalidate the relationships found between curvature and thickness as the same observer recorded all measurements It is also probable that differences exist between samples even when readings are taken by the same observer on one instrument and possible that some intrinsic difference occurs between national populations (the results obtained here are compared with those from the U S A Australia and Denmark)

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CORNEO CONJUNCTIVAL CHANGES IN UREMIA

Influence of renal allotransplantation

BY

N EHLERS F KRUSE HANSEN H E HANSEN
and O A JENSEN

The present study is based on a material comprising 78 patients Fifty one patients had uremia 8 had well functioning renal allografts and 7 suffered from hyperparathyroidism Twelve patients with corneo conjunctival changes but normal renal function and normal calcium metabolism served as a control group

Clinically and histopathologically the corneal changes resembled the limbus girdle of Vogt while the conjunctival changes were those of a pinguecula with small whitish amorphous or crystalline precipitates of Ca salts probably phosphates Distinct changes were found in 50% of the patients with uremia The occurrence could be correlated with the duration of the renal disease but not with the duration of the uremia or the nature of the renal disease Within the group of patients with uremia no correlation with serum creatinine creatinine clearance serum calcium or alkaline phosphatase could be demonstrated The degree of changes increased with increasing serum phosphate The changes were not influenced by the number of hemodialyses but a curative effect of renal transplantation was demonstrated

Finally the nature and the pathogenetic possibilities of these changes are discussed and it is concluded that except for the local presence of proteins and calcium and the elevated serum phosphate concentration nothing definite is known

Key words corneo conjunctival changes – *hemodialysis* – limbal changes – renal transplantation – *uremia*

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Although in the earlier literature corneal calcifications have been described in hyperparathyroidism vitamin D intoxications and sarcoidosis the recent interest in uremic corneo conjunctival changes was initiated by Abrams (1966) who reported corneal changes in 13 among 20 patients treated by intermittent hemodialysis for renal failure The changes varied in degree from a white limbus girdle of Vogt to that of pronounced corneal calcifications The patient who led Abrams to this study had irritated red eyes A similar conjunctival injection was reported in acute and chronic renal failure by Berlyne & Shaw (1967) in 15 patients with a raised serum inorganic phosphate but a normal or low serum calcium Abrams found no consistent relationship to serum levels of calcium phosphate or alkaline phosphatase

The following year Berlyne (1968) described a "microcrystalline conjunctival calcification" in 13 patients with renal failure 12 of these showing in addition a "limbal arc calcification Only 3 of the patients had red eyes and it was emphasized that in the majority of patients with advanced chronic renal failure the eyes are white Histologically Berlyne demonstrated calcium and phosphate precipitates in the conjunctiva

Schumacher & Scheler (1969) in 15 cases of chronic renal failure treated by hemodialysis reported calcifications in the cornea and conjunctiva The conjunctival changes were described as typical pingueculae with only a slight conjunctival injection and small calcifications The corneal changes were similar to Vogt s white limbus girdle In addition it was mentioned that 3 out of 6 patients with renal failure but not treated by dialysis showed the same changes

Similar observations were reported by Easterbrook & Mortimer (1970) in 13 cases of chronic renal failure and by Harris et al (1971) in 18 patients The possible influence of renal transplantation was reported by Caldeira et al (1970)

Table I
Renal disease sex and age of the 59 cases of the present material

Kidney disease	No of patients	Males	Females	Age average (years)
Glomerulonephritis	22	13	9	37
Chronic Pyelonephritis	21	8	13	45
Other	16	8	8	35
Total	59	29	30	

Material and Methods

The study comprised a total of 78 patients Fifty one patients had uremia i e creatinine clearance less than 10 ml/min Eight patients had been treated by renal allo transplantation The distribution according to renal disease as well as to sex and age of these 59 patients is shown in Table I Twelve patients with similar corneo conjunctival changes but with normal renal function and normal calcium metabolism served as a control group Data from these 71 patients are presented in Table II Finally 7 patients with hyperparathyroidism were included in the study The studies were made in the period September 1969 to September 1971

The corneo conjunctival changes were evaluated by slit lamp biomicroscopy and arbitrarily graded from – to ++ Vital staining for calcium was attempted with Alizarin red S Nuclear fast red Naphtochrome green and Tetramethyl murexid but remained unsuccessful The medical examination comprised determination of serum creatinine creatinine clearance serum calcium and phosphate and serum alkaline phosphatase Patients on a regular hemodialysis program were treated twice weekly for 19 hours in a Gambro parallel flow artificial kidney As mentioned 8 patients had received a renal graft before the first examination while 7 were transplantated during the examination period All patients with uremia were given a diet containing 30–40 g protein each day and most of these had Ca resin 15–45 g daily

Histopathological examination comprised conjunctival biopsies from 7 patients with renal failure 1 with hyperparathyroidism and 1 from the control group Two eyes from patients in the control group were enucleated because of malignant melanoma of the uvea.

6 biopsies were fixed in absolute ethanol 1 biopsy and the two eyes were fixed in 4% sodium phosphate buffered neutral formaldehyde The fixation was carried out for 24 hours at 4 C

Routine paraffin technique was employed Deparaffinized hydrated sections were stained with hematoxylin eosin the van Gieson stain by the Alizarin red S method (Dahl 1952) the von Kossa method (von Kossa 1901) and by the murexid staining method (Kaufman & Adams 19 7) Unstained sections were examined in polarized light Frozen sections of formalin fixed material were made of one of the eyes (Lab No 1 1 70) followed by Oil red O Sudan black B and Luxol fast blue staining

Results

1 Clinical appearance

In chronic renal failure changes were found in the conjunctiva and in the cornea (Fig 1) The conjunctival changes consisted of subepithelial whitish deposits in the interpalpebral area mostly as discrete amorphous deposits but sometimes with small clear crystal like precipitates The appearance was usually very similar to a pinguecula Most often the corneal changes were indistinguishable from a white limbus girdle of Vogt but in more advanced cases they suggested an incipient band keratopathy One case showed the round

Table II

Data for 51 patients with uremia 8 patients treated by renal transplantation and 12 control patients For comments see text

Condition of the patients		Patients in uremia				Patients treated by transplantation	*Control* patients
Corneal calcifications grade		–	(+)	+	++	– *to* (+)	+ *to* ++
No of patients		15	11	15	10	8	12
Age (average)		35	45	45	34	32	65
Duration of renal disease (months) (average)		42	26	144	186	–	–
Duration of uremia (months) (average)		9	12	18	12	–	–
No of hemodialyses (average)		20	23	40	40	–	–
Se Creatinine mg/100 ml (average)		9.9	10.8	8.7	12.9	1.8	0.8
Creatinine clearance ml/min (average)		3.6	3.9	2.7	2.1	48.0	90.0
Se Calcium (mg/100 ml) (normal range 9.0–10.8)	average ± s d	8.61 ± 2.11	9.01 ± 0.97	8.91 ± 2.34	9.71 ± 1.06	9.71 ± 0.70	9.70 ± 0.23
Se inorganic Phosphorus (normal range 2.[illegible]–4.7)	average ± s d	6.01 ± 2.01	6.90 ± 2.44	6.90 ± 1.77	10.70 ± 3.55	3.21 ± 0.53	3.40 ± 0.38
Se alkaline phosphatase (K A units)	average ± s d	18.1 ± 11.7	10.7 ± 3.1	14.8 ± 8.2	13.7 ± 4.7	8.5 ± 1.7	–
Se *Calcium* × Se inorganic Phosphorus	average ± s d	49.8 ± 12.8	61.0 ± 22.3	66.2 ± 18.6	102.8 ± 34.7	31.0 ± 5.[illegible]	33.9 ± 4.5



Fig 1
Appearance of corneo conjunctival changes in slit lamp

holes characteristic of band keratopathy The conjunctival and corneal changes usually occurred together with either of the two dominating how ever Conjunctival injection was not a typical finding Only one patient in the present material demonstrated red renal eyes

This was a man aged 45 ears with uremia due to chronic pyelonephritis He had not been treated with extra orporal dialysis at the time of examination Slit lamp biomicroscopy revealed well developed corneal and conjunctival changes with fine crystalline subepithelial precipitates In addition well marked hyperemia of the bulbar conjunctiva was present Serum creatinine was 17 1 mg 100 ml creatinine clearance ~3 ml min serum calcium 8 9 mg/100 ml serum phosphate 11 1 mg/100 ml Microscopic examination of a conjunctival biopsy (Lab No 749 /0) showed positive staining for calcium in the epithelial and subepithelial tissue

2 Occurrence and frequency of corneo-conjunctival changes in uremia

The present material comprised patients with various renal diseases (Table I)

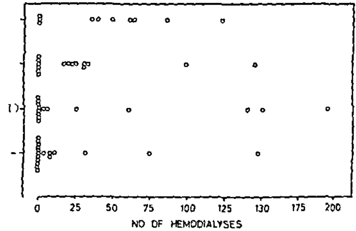


Fig 2
Diagram of grade of corneo conjunctival changes versus number of hemodialyses

An analysis revealed no differences between the various renal diseases with respect to corneo conjunctival changes From Table II it appears that 50% (25 of 51) of the patients with uremia showed distinct changes and 20% severe changes The changes were found mainly in patients with renal disease of long duration but great variations occurred The present material revealed no correlation between the duration of the terminal uremia and the severity of the corneo conjunctival changes

No correlation with serum creatinine or creatinine clearance was noted Similarly no correlation with serum calcium and serum alkaline phosphatase could be demonstrated whereas serum inorganic phosphate was increased in cases with severe changes (Table II) The increased serum Ca/P product in the patients with the most severe changes contains no more information than the elevated value of serum inorganic phosphate

3 Influence of hemodialysis and transplantation

Among the patients with uremia no correlation between the number of hemodialyses and the corneo conjunctival changes could be demonstrated (Fig 2) in spite of the apparent correlation that might be suggested from Table II

Eight patients with well functioning renal allografts for an average of 26 months (3 60 months) were studied (Table II) All showed changes graded as – to + Seven patients were examined before and after renal allotransplantation One showed no changes either before or after transplantation and 1 with changes graded as + + was unaltered 3 months after transplantation The remaining 5 cases showed a marked decrease or disappearance of the corneo conjunctival changes

The influence of renal function upon corneo conjunctival changes is illustrated by a 24 year old woman suffering from acute glomerulonephritis When first examined the patient had uremia having rejected graft No 1 which had been functioning for 18 months The corneo conjunctival changes were graded as ++ When examined 3 months after successful retransplantation no changes were present Two months later graft No 2 was rejected and 7 months later corneo conjunctival changes had reappeared

4 Hyperparathyroidism

Seven patients with hyperparathyroidism were examined Four cases showed no changes and the remaining 3 only to a very slight degree All 7 patients had normal renal function (average creatinine clearance 97 ml/min) elevated serum calcium (average 12 0 mg/100 ml) and low serum phosphate (average [illegible] mg/100 ml)

5 Control material

Twelve patients with similar corneo conjunctival changes were examined for renal function All showed normal serum creatinine creatinine clearance serum calcium and phosphate (Table II)

Table III
Survey of cases examined histopathologically

Lab No	Patient	Age	Tissue	Fixative	Epith deposits	Subepith deposits	Elastosis
[illegible] 70	RF	51	Conj	Formalin	(+)	(+)	+
4 9 0	RF	47	Conj	abs alc	–	+++	–
11 0	RF	4[illegible]	Conj	abs alc	–	–	++
1[illegible] 0	RF	[illegible]3	Conj	abs alc	+	+++	+
4[illegible] 0	RF	44	Conj	abs alc	+	+++	–
[illegible] 0	RF	54	Conj	abs alc	–	+++	+++
1 0	RF	45	Conj	abs alc	+	+++	+++
5 4 0	H	47	Conj	abs alc	–	–	+++
9[illegible] 0	C	[illegible]4	Conj	abs alc	++	+++	+++
1 1 0	C	63	Eyeball	Formalin	–	(+)	–
13 0	C	60	Eyeball	Formalin	–	–	–

Symbols RF renal failure H hyperparathyroidism C control group
The changes were arbitrarily graded from (+) to +++

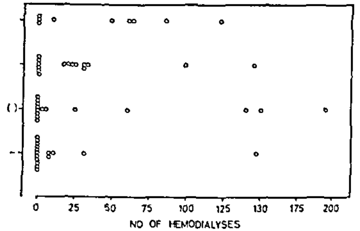


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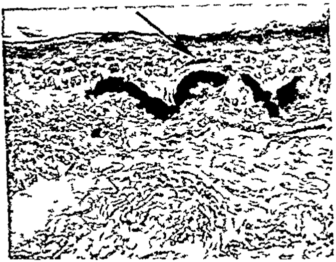


Fig 4
Epithelial (arrow) and subepithelial deposits von Kossa s stain Lab No ı12/70 × 275

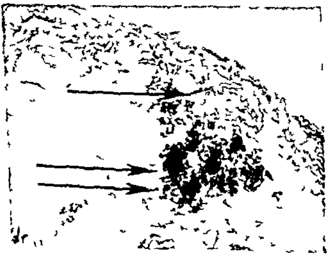


Fig 5
Elastosis (arrow) and subepithel al calcifications (double arrow) Murexid staining Lab No ›0 0 × ᵃ 5



Fig 3

Duplication of conjunctiva with subepithelial von Kossa positive deposits
Lab No 459 70 × 100

6 Histopathological changes

The results are summarized in Table III In all except one case of renal failure strongly stained subepithelial calcium deposits were found (Fig 3) In the formalin fixed biopsy the deposits were less prominent but in addition discrete epithelial deposits were seen Slightly more pronounced epithelial deposits of calcium were observed in three further biopsies mostly in the basal cells and only in areas above subepithelial deposits (Fig 4) Elastosis of the connective tissue morphologically identical to the changes seen in pingueculä were found in 5 of the 7 biopsies in 3 to a heavy degree These changes were often in the calcium infiltrated areas (Fig 5) and mostly reaching beyond these In addition elastosis was observed in areas other than those infiltrated by calcium

The patient with hyperparathyroidism showed only elastosis but no calcium deposits whereas two in the "control group had calcium deposits and one elastosis

The formalin fixed eyeball from one of the control patients showed only discrete deposits subepithelially in the limbal area of the cornea In some cases the calcium infiltrated areas could be detected by a strong basophilia but often only the special stainings revealed the deposits Birefringence was in no case observed The fat stainings were negative in the eyeball examined

In the one case where red renal eyes" were observed no increased leukocyte infiltration was found

The histological findings were similar to those published by others (Berlyne & Shaw Berlyne Caldeira et al Easterbrook & Mortimer) but with two exceptions i e we found no increased leukocyte infiltration in our case of red renal eyes as reported by Berlyne & Shaw and no crystals as described by Berlyne The changes found in the biopsy from the control patient aged 64 years were completely similar to the changes in the much younger group of patients with renal failure The quantitative lesser changes in the other control patient (Lab No 171/70) may be due to the formalin fixation as it is seen that the changes in the formalin fixed conjunctival biopsy (Lab No 26//70) from one of the patients with renal failure were less pronounced than those fixed in absolute ethanol

The elastosis seen in the controls and in the uremic patients was identical and indistinguishable from the elastosis seen in cases of pinguecula The histopathology can thus support the hypothesis that the changes in patients with uremia may be considered as accelerated age changes

The product of serum calcium and serum phosphate was introduced by Berlyne (1968) as a parameter connected to corneo conjunctival changes in uremic patients and used by subsequent authors It presupposes a simple physico chemical precipitation of calcium phosphate and ignores a possible function of proteins the presence of which is evident clinically and histopathologically (elastosis) The occurrence of more complicated chemical reactions is probable

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Discussion

In the present material conjunctival changes have been biomicroscopically and histopathologically very similar to a pinguecula with small subepithelial calcifications and occasionally a slight injection, while the corneal changes have been indistinguishable from the Vogt limbus girdle This description is in agreement with Schumacher & Scheler (1969) whereas evidently Abrams (1966) and Berlyne & Shaw (1967) observed more severe changes The red renal eyes" which were described by the latter authors occurred only once in the present material

Thirty six of 51 patients (72 %) with uremia irrespective of the nature of the renal disease demonstrated varying degrees of corneo conjunctival changes The changes are thus common in uremia Abrams observation that the changes are more severe in chronic glomerulonephritis cannot be supported

Similar changes especially corneal were seen in a control group of patients which proved to have normal renal function (Table II) The average age of this latter group was however significantly higher than that of the different groups of patients with uremia This raises the question whether the changes seen in uremia may be considered as accelerated age changes The present material showed a correlation between the duration of renal disease and the degree of corneo conjunctival changes

Previous authors have suggested a correlation to the duration of dialysis treatment which in accordance with Abrams could not be found in the present study

Caldeira et al (1970) reported on one patient with uremia treated by kidney transplantation The corneo conjunctival changes tended to disappear In the present study 15 patients have received a kidney transplant Eight patients were examined only after successful grafting and showed no or minute changes (Table II) Seven patients were grafted during the examination period and 5 showed a marked decrease or disappearance of the changes One with changes graded as ++ was unaltered and the last one had no changes either before or after renal grafting From these observations it appears that the corneo conjunctival changes are caused by a failure in renal function This function is not substituted by dialysis (Fig 2)

The corneo conjunctival changes showed no consistent relationship to serum calcium or alkaline phosphatase whereas an elevated serum phosphate seems to be characteristic as previously reported by Berlyne & Shaw (1967) Berlyne (1968) Schumacher & Scheler (1969) Easterbrook & Mortimer (1970) and Harris et al (1971)

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PUS AND MUCUS AROUND SUTURES FOLLOWING CATARACT EXTRACTION

Studied by Vital Staining with Tetrazolium Alcian Blue Mixture

BY

M S NORN

66 cataract extracted eyes have been examined for presence of mucus and pus around sutures by vital staining with a mixture of tetrazolium and alcian blue

Bared sutures are always enveloped in mucus Pus is more often seen around conjunctival sutures (57 %) than around perforated corneo scleral sutures (29 %)

The incidence of pus around sutures seems to be independent of the suture material used (7–0 silk against 6–0 collagen) and the postoperative interval (two days to four months) The incidence rises in relation to infectious conjunctivitis

Mucus is found in diastases after gaping conjunctival wounds Pus is contained in 45 % of them

Micro abscess at suture was noticed in 9 % of the eyes

Key words vital staining – tetrazolium – alcian blue – sutures – cataract extraction – mucus – pus

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scleral incision was sutured by five knotted silk sutures 7–0 and the conjuncti val incision by a continuous 7–0 silk suture

In 16 cases 6-0 collagen sutures were used knots corneosclerally and knots or continuous suture in the conjunctiva

In most cases vital staining was performed 7 or 8 days after the operation In 9 cases the interval was from 2 to 5 days in 16 cases more than 12 days Maximum was 4 months

Result

As a general rule *no* conjunctiva covered sutures become stained All conjunc tival and all corneoscleral sutures perforating the conjunctiva became en veloped in mucus or pus The diastases after conjunctival wounds forming grooves in the conjunctiva often contain mucus or pus

Knotted Corneoscleral Sutures

In the 66 cataract extracted eyes a total of 321 knotted corneoscleral sutures had been employed On the examination 124 of these had perforated the con junctiva with a single end or more of the suture material sticking out from the conjunctiva Except in one case the free suture end was plainy seen to be

Table I

A Number of eyes with mucus or pus around suture or in conjunctival groove a total of 66 eyes
B Incidence of pus in per cent of total number with mucus or pus
C Number of sutures or conjunctival grooves
D Number of sutural elements or grooves with mucus or pus
E Incidence of pus in per cent of (D)

	A	*B*	*C*	*D*	*E*
c rneoscleral suture	53	40	321	1[illegible]5	29
conjunct val suture	13	85	90	37	57
conjun tival g oc v	33	55	44	44	45

Introduction

Mucus and pus are often seen on the dressing and around sutures after cataract extraction Are such coatings around sutures harmful? Do they contain bacteria? Or *is it sterile mucus that envelops the sutures* thus reducing the mechanico irritant effect of these?

These problems can be elucidated to some extent by vital staining with a mixture of alcian blue iodonitrotetrazolium Alcian blue is a specific dye which stains only mucus while tetrazolium stains structures having reducing properties in the first place degenerate neutrophilic leucocytes Using this mixture mucus assumes a blue colour and pus a red

All humans have a mucous thread in the inferior conjunctival fornix In normal eyes this is stained blue by the stated mixture In cases of infectious conjunctivitis on the other hand the mucous thread is stained both red and blue The red sections by no means smaller than the blue consist of nests of neutrophilic leucocytes Using this dye mixture we can thus distinguish between a sterile, normal conjunctiva and a bacterially infected one (conjunctivitis) (Norn 1971 1972)

Method

The vital *stain employed is composed as follows*

iodonitrotetrazolium	0 1 g
alcian blue	25 mg
distilled water to	10 g
aseptically prepared	

From a bottle mounted with a needle (0 5 × 16 mm) to be used only once 0 01 ml of the stated vital stain mixture is instilled so as to fall on the upper lateral part of the bulbar conjunctiva while the patient is looking down and nasally After a latency of not less than 4 minutes – sufficient for enzymatic reduction to the red formazan – the patient s eye is examined in the slit lamp If fairly large amounts of mucus are present these are removed by means of a *cotton swab to render possible examination also of the underlying structures* In some instances sutures are cut off and subjected to microscopy

Material

The investigation comprised a total of 66 patients subjected to cataract extraction

Limbus based conjunctival flap was employed in most cases The corneo

Conjunctival Suture

No more than 20 conjunctival sutures were studied the majority having been removed by the time of the investigation Eight sutures were continuous A total of 37 accumulations of mucus or pus were seen as a continuous suture may display coatings of the two free ends and coatings on the part of the suture situated on the surface of the conjunctiva between the points of two stitches (Fig 1F) As where the corneoscleral sutures are concerned lumps of pure mucus and lumps containing a rather considerable amount of pus may interchange irregularly in the same eye

Pus was found more frequently around the conjunctival sutures than around the bared corneoscleral sutures (in 57 % against 29 % of the mucous coatings) The difference is statistically significant ($p < 0.02$) The suture material used (silk or collagen) yielded no difference

Diastasis after Conjunctival Wound

The conjunctival wound is often maladapted after a cataract extraction One seems to look directly on the exposed sclera At the time of the investigation the sclera was however covered by conjunctival epithelium the bottom of the groove being not stained by fluorescein

Mucous coatings are often found in the groove Pus was demonstrated in 45 % of these coatings i e the incidence of pus was between that for the conjunctival and that for the exposed corneoscleral suture

Mucous Thread in Inferior Conjunctival Fornix

An amount of pus in the mucous thread corresponding to or exceeding that of mucus raises suspicion of infectious conjunctivitis This was so in 30 % of the 66 eyes

Pus around sutures and in grooves is more frequent in association with signs of bacterial conjunctivitis (in 51 % of infected against in 32 % of non infected $p < 0.05$)

Micro-Abscess in Cornea

A small corneal abscess around the bared corneoscleral suture at the limbus was seen in 9 % of the eyes (a total of 9 abscesses) Two of these abscesses were stained red The remaining were not stained presumably because the dye could not penetrate through the epithelium into the accumulated pus

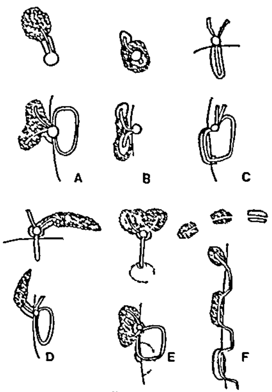


Fig 1

Mucus and pus around sutures Different examples from 66 cataract extractions A-E corneoscleral knotted sutures F continuous silk sutures in the conjunctiva The obliquely hatched areas represent pus and the "woolly areas mucus The upper row shows the suture from the front side and the lower row imaginary sections with the surface to the left

enveloped in mucus or mucous pus Pus was detectable in 29 % of these cases In 11 % there was as much pus as mucus while in 2 % only pus and no mucus was found around the suture In 40 % of the eyes with mucus enveloped corneoscleral sutures one or more sutures presented pus (Table I)

Fig 1 illustrates various examples of the relation between mucus and pus in partially perforated corneoscleral sutures partly from the front side and partly in imaginary sections

The pus is deposited the nearest to the suture and the mucus peripherally on the pus Pus may be found along the free suture end (B) around the knot (F) or along the deep suture which is exposed at the limbus (C)

After cutting of a suture pus may occasionally be seen some way into the suture canal Repeated staining may in some instances disclose pus through the whole length of the canal while in others the canal seems to be free from pus

The incidence of pus around the corneoscleral suture seems to be independent of the time interval from the operation

sutures rarely give complications Such complications if occurring may become dangerous e g in corneal grafting

A careful atraumatic surgical technique may reduce the risk of infection of the mucus always enclosing bared sutures and filling up grooves after gaping conjunctival wounds

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Microscopy

Microscopy of four vital stained cut off corneoscleral sutures confirmed that the red colour centrally around the suture is due to myriads of neutrophilic leucocytes while the surrounding blue colour comes from mucous fibrils.

Discussion

Why does pus accumulate around many of the bared sutures in the conjunctival sac?

The reaction may be due to a *toxic* action of suture material The fact that the suture material is surrounded by pus in some cases only while neighbouring sutures are free goes against this hypothesis

Sutures may cause *mechanical* irritation and thus attract leucocytes Against this explanation argue the observations that pus may in fact be found in the least traumatized regions e g in the middle of a continuous suture (Fig 1F) and be absent at a greatly projecting knotted suture end

The pus may be due to *bacteria* which find a fertile soil in the mucus around the sutures

This latter hypothesis is borne out by the fact that pus has been found particularly in the cases with additional signs of bacterial infectious conjunctivitis.

Aronson et al have shown that the reaction around corneal sutures in connective tissue are rarer in germ free treated guinea pigs than in normally bred animals This suggests a bacterial influence on the suture reaction under the surface

The present investigation is concerned with infection on the surface of a mucous membrane around sutures It is therefore not directly comparable to subepithelial infection

Special conditions prevail in the conjunctival sac dependent on tear flow lysozyme content of the tears mucus envelopment of sutures bacterial flora of the conjunctiva and perhaps impaired resistance of the mucus around the sutures and in the grooves

The result may be presence of pus in the mucus which possibly may develop into abscess formation around the fairly deep parts of the suture

Knotted silk sutures remain for a long time in the limbal region often partially bared In 30 cataract extracted patients with 131 silk sutures 35 persistent sutures were found six months later among which 18 were bared (Norn 1968)

It may seem surprising that the pus containing mucous coatings on the

ades however attention has increasingly focused on the delayed – or cellular – type of hypersensitivity especially regarding autoimmune diseases and graft rejection A more exact and quantitative study of this aspect of immunopathology has nevertheless been impeded until recently because of lack of sufficiently sensitive and specific *in vitro* assays (Gowans 1965 Holm 1969 Bendixen & Søborg 1969)

It is generally agreed that the effector cell in the delayed hypersensitivity reaction is the so called immunologically competent small lymphocyte. Much of the natural history and function of these cells is as yet poorly understood but in broad terms it can be stated that when triggered in a culture by a suitable antigen, they undergo a series of intrinsic reactions including nucleic acid synthesis which result in an accelerated proliferation of immunologically activated blastlike or transformed lymphocytes (Cronkite & Chanana 1968 Sipe et al 196? Oppenheim 1968)

Concurrent with the experimental and clinical evidence of the dominant role of the cellular hypersensitivity in graft rejection, various ways of suppressing it have been explored In widest use are the corticosteroids often supplemented or eventually replaced by stronger and more specific cytostatics A common feature of these drugs is that they possess moreover an *anti inflammatory* action which makes the clinical evaluation of their immunosuppressive properties less reliable (Elliott 1971)

Antilymphocyte globulin is at the present time mostly an experimental tool due to its toxicity although it does have promising clinical perspectives In any case its usefulness will always be vitiated by the risk of parenteral protein administration

Ionizing radiation

The radiosensitivity of the lymphocyte has been utilized in experimental transplantation research from early in this century but the radiation dose necessary to kill a major fraction of the lymphocytes has invariably resulted in irreversible bone marrow and gastrointestinal damage when applied in the form of whole body radiation Less extensive procedures such as irradiation of the spleen and thymus parenteral administration of radioactive isotopes and irradiation of the graft and/or graft bed prior to transplantation have all proved to be considerably less helpful in prolonging graft survival (Cronkite & Chanana 1968)

The possibility of irradiating the blood and lymph outside the body has been thoroughly investigated by Cronkite and his colleagues Due to the selective radiosensitivity of the lymphocytes the most obvious experimental application of this technique has been in the study of the kinetics of these cells and the reaction of the lymphoreticular organs to lymphocyte depletion As a clinical tool it has been evaluated in patients with chronic lymphatic leukaemia and for the purpose of immunosuppression (Cronkite & Chanana 1968 Chanana et al 1969 Cottier et al 1964 Weeke et al 1970 Pers n t al 1969)

A t radiation of human lymph – by cannulation of the thoracic duct – is a far fr m a y p ocedure the following description will account only for extracorporeal irradiation of the blood (ECIB)

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EXTRACORPOREAL IRRADIATION OF THE BLOOD AND CORNEAL TRANSPLANTATION

A survey with a report of the first case

BY

ERIK KROGH, M.D. and EVA WEEKE, M.D.

A brief discussion of the cellular – delayed type – hypersensitivity with special regard to graft rejection is given. Various methods of suppressing this process are mentioned, followed by a description of one of the more specific and clinically promising methods – namely extracorporeal irradiation of the blood (ECIB). The first known case in which ECIB was performed prior to and after a corneal transplantation in a previously transplantated eye is reported. The favourable result, although standing alone and not conclusive, should stimulate further controlled investigation.

Key words: extracorporeal irradiation of the blood – ECIB – corneal transplantation – cellular hypersensitivity – delayed type hypersensitivity – graft rejection – immunosuppression.

Introduction

Cellular hypersensitivity

The classical concepts of allergy are founded on the knowledge of the reaction between the antigen and a specific *circulating antibody*. In the past few dec-

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monstrated in the same experiments (Polack 1965 Leibowitz & Elliott 1966 Cleasby et al 1966)

A suitable treatment with ECIB will however bring about a depletion solely of the immunologically activated or potentially activated lymphocytes which apparently do not play a major role in other forms of inflammation and will not result in a reduction of the concentration of the circulating im munoglobulins A clinical trial with ECIB was therefore found natural in a case with a probable immunogenic opacification of a corneal graft and a pre sumed high risk for a new graft

However it is probable that a small in itself ineffective and widely non toxic dose of azathioprine as an adjunct to ECIB tends to prolong the graft survival (Cronkite & Chanana 1968 Weeke et al 1970) Furthermore ECIB leaves the germinal centers intact or even stimulates them to increased mitotic activity in contrast to the action of corticosteroids (Cottier et al 1964)

A pure ECIB trial the most satisfactory procedure from the experimental point of view could therefore very well be clinically suboptimal With the long monotonous pretransplantation period and the doubtful *result in mind* it was considered impossible not to combine the irradiation with the pharmacologi cal addition outlined above

Case history

The patient a woman aged 57 presented a total dense leucoma cornea in the right eye after corrosion with ammonium hydroxide in 1964 Intense medical treatment and a flush fitting lens caused only a temporary amelioration, and a lamellar keratoplasty resulted in a speedy opacification and neovascularisation of the graft

This patient was admitted to the ophthalmological department in April 1971

The visus oculi dxt was finger counting ad oculum The eye was nearly pale and the



Fig 1
The right eye before transplantation

Clinical extracorporeal irradiation

The technique is simple In brief the blood from the patient s arterio venous shunt (or fistula) is led through an external blood tube passing the radiation field of the therapy unit In most cases a blood pump has to be used to obtain a constant blood flow which is measured as the *passage time of a microbubble of air over a known length of blood* tube

The transit dose is defined as the radiation dose received by any item while in transit through the radiation field The number of blood volumes radiated is calculated from the measured blood flow rate through the irradiator and an assumed blood volume of 7 % of total body weight The total radiation dose is calculated as a product of transit dose and number of blood volumes radiated (Slatkin et al 1963 Sipe et al 1965)

Usually ECIB is given 6–10 hours per day 3–5 days a week for about 3 weeks. During the treatment period the patient is anticoagulated Infection rarely presents a serious problem

In 80 uremic patients reported by Weeke (1971) the lymphocyte concentration was reduced to 30 % of the pretreatment value during ECIB After cessation of radiation the lymphocyte concentration usually remains at a lower level than the pretreatment value for several months (Weeke et al 1970)

ECIB and corneal transplantation

The irreversible opacification of a corneal graft is a result of an inflammatory process whose specific etiology often will elude a pure clinical guess That some cases are due primarily to an antigen antibody reaction is however beyond doubt (Elliott 1971)

Investigations concerning the role of *circulating* antibodies in corneal graft rejection have largely emphasized the following points 1) There is – in normal *corneas – an abundance of immunoglobulins* (Allansmith & O Connor 1970) 2) Circulating anticorneal antibodies will often be found in animals having received a corneal allo or xenograft and the titre will sometimes rise in the posttransplantation period 3) Nevertheless this rise cannot be correlated with the appearance or the speed of opacification of the graft (D Ermo et al 1966 Leibowitz & Luzzio 1961 Tsutui & Watanabe 1961)

Attempts to inhibit or treat corneal graft rejection with corticosteroids or *more* specific cytostatics in experimental conditions in which the opacification presumably is of immunological origin will often show rather convincing results However as mentioned earlier the general anti inflammatory action of these drugs precludes an exact conclusion regarding their specific immunosuppressive value

This fact alone should not of course impede a clinical trial as most cases of human corneal graft rejection probably are of multifactorial origin But the severe toxicity of an effective dosage of the most widely investigated cytostatics for systemic use i e 6 mercaptopurine and azathioprine is clearly de

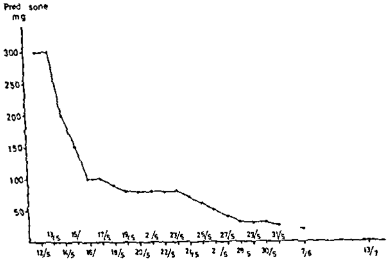


Fig 3
Prednisone administration in the postoperative p riod

during the irradiation – an unexpected event which might indicate an immunological genesis of the inflammation

Towards the end of the preoperative irradiation the patient had to be anticoagulated because of increasing obstruction of the shunt flow

On May 19 1971 an 8 mm penetrating corneal transplantation was performed After trephining of the host d sc the pupil was found mydriatic due to posterior synecchias which became visible by slit lamp examination postoperatively Miotics had no effect at all The lens seemed normal The donor cornea was fixed with a continuous suture

On the day of operation the patient received 300 mg of azathioprine by mouth followed by 50 mg daily a dose to be continued for several months A few hours post operat vely 300 mg of prednisone was given by mouth the subsequent dosage is plotted in Fig 3

In the postoperative period a new series of ECIB was carried through (Fig 2) whereafter the shunt was removed and the anticoagulant therapy stopped without compli ations Fig 4 shows the eye on the 28th postoperative day

The postoperative course was c mplicated by an iris prolapse on the 3rd day ap parently due to a slackening of the s ture The prolapse was treated immediately with e c n and esuturing On the 30th postoperati e day an attack of acute glaucoma d el p d presumably caused by a newly formed anterior synecchia. An iridencleisis t g ther w th a partial loosen ng of the anterior synecchia was performed whereafter the t ns n n mal zed completely without med cal treatment

The ual acuity of the right eye rose in a few days after the keratoplasty to 6/12 with the us of a stenopeic hole Very soon after th iridencleisis a visual acuity of ( ) w th 00 sph combined with – 3 00 cyl (110) was obtained When the effect f th la ge pupil was damped with a stenopeic hole the acuity was 6 6

palpatory tension normal In the slit lamp a densely vascularized corneal leucoma was seen Only a small peripheral sector of the anterior chamber could be visualized The pupil lens and vitreous body were hidden from view, and ophthalmoscopy yielded only a *red fundus reflex* (*Fig 1*)

The visus oculi sin was 6/6 and the eye in every respect normal

The general state and especially the coagulation and the hematological parameters were optimal

As the prognosis for a new keratoplasty seemed to be poor the case was considered suitable for an experimental evaluation The patient who was interested in both a cosmetically and a functionally better result consented at once fully informed of the experimental nature of the procedure

A Scribner arterio venous shunt was established in the left forearm and the ECIB was begun with a 137 Cs source for periods of 4–5 hours a day and resulted in the de monstrated decline in the lymphocyte concentration (Fig 2) Neither the concentration of thrombocytes nor of polymorphonuclear leucocytes fell to any embarassing degree

The vessels in the leucoma demonstrated a marked reduction of the blood content

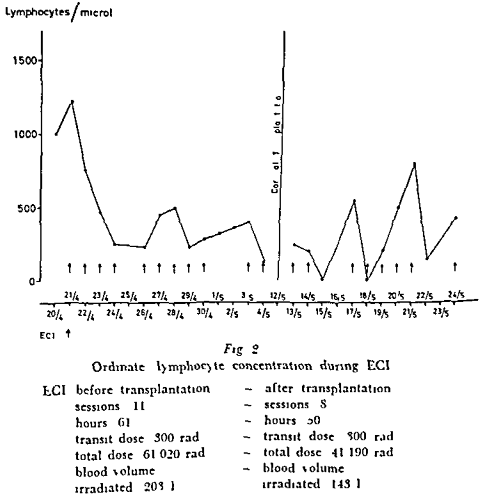


Fig 2

Ordinate lymphocyte concentration during ECI

ECI before transplantation	– after transplantation
sessions 11	– sessions 8
hours 61	– hours 50
transit dose 300 rad	– transit dose 300 rad
total dose 61 020 rad	– total dose 41 190 rad
blood volume irradiated 203 l	– blood volume irradiated 143 l

Discussion

It seems justified to state that the second corneal transplantation in this patient demonstrated a much more favourable course than the first with respect to reactions of possibly immunological origin Any firm conclusion regarding the role of ECIB in this outcome naturally is not possible for various reasons some of which are the following 1) There exists no safe clinical observation by which an opacification of the cornea – the patient s own or a graft – can be classified as antigen antibody dependent 2) Even if the rejection of the first – lamellar – transplantate showed itself to be of immunological nature the same factors would not necessarily be operative in a second transplantation and a new antibody response with a clinically detectable action would not necessarily be triggered 3) Finally in the case of immunological activation of clinical significance the combined anti allergic and anti inflammatory actions of the drugs employed could alone account for the good result

In fact the reduction of the blood content in the vessels of the leucoma which occurred when ECIB was given alone preoperatively is the only evidence of its possible effect – and therefore of the immunogenesis of the condition

The only possible way to reach a safer conclusion is a controlled clinical investigation – preferably combined with a laboratory correlate i e an *in vitro* test for sensitized lymphocytes followed up during the immunosuppressive treatment Such a trial is under preparation

ECIB proved to be without serious complications which is in keeping with other clinical experience (Weeke et al 1970) Shunt problems are minimal when handled by experienced personnel In fact the only serious drawbacks of this method are that it is time consuming and that the patient – for the time being – must be hospitalized for most of the irradiation period

Addendum

An increa ng number of reports concerning the positive influence of antilymphocyte gl bulin on exper mental corneal graft survival have been published during the last year The results generally seem to emphasize the importance of cellular hypersensi t vity in k rat plasty thus supporting the hypothesis of the present paper

See f instance Polack F M Townsend W M & Waltman S (1979) *Amer J Ophth* 3 5 55

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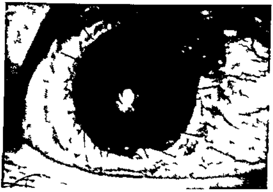


Fig 4
The right eye 28 days after penetrating corneal transplantation

Apart from a short period 3 months after transplantation with epithelial bullous edema and slight haziness in the anterior half of the vitreous body which cleared up with local steroid treatment the eye has maintained this acuity up to the present

The present state of the transplanted eye – six months postoperatively – is as follows The visual acuity is 6/6 with – 3 00 sph combined with a stenopeic hole Examination with the keratometer shows pronounced irregular astigmatism With the slit lamp a perfectly adapted donor disc with normal epithelium and stroma is seen A discrete vascularisation of the host cornea is visible. On the endothelial surface of both donor and host cornea are seen slightly pigmented remnants of precipitates which followed some days after the iridencleisis (Fig 5)

The anterior chamber is of normal depth and without any aqueous flare The pupil is still dilated and several peripheral anterior synecchias are visible The lens is clear The applanatory tension is 14 mm Ophthalmoscopy yields a slightly hazy view of a normal fundus Perimetry with a white object 10 1000 is normal

The general state did not change apart from a temporary ventricular dyspepsia related to the treatment with prednisone An X ray examination showed a completely normal ventricle and duodenum

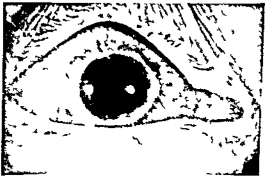


Fig 5
The right eye six months after penetrating corneal transplantation

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RETROBULBAR NEURITIS AS AN EARLY SYMPTOM OF GUILLAIN BARRE SYNDROME

Report of a Case

BY

E NIKOSKELAINEN M D and P RIEKKINEN M D

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Key words optic neuritis – Guillain Barre syndrome – demyelination – autoimmunization

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et al 1970) Asbury et al (1969) also stress the concept that the symptoms and lesions can most often be explained as polyradiculoneuronitis of peripheral nerves In fact most cases (80 %) do corroborate this description but some times unusual clinical features can be found Elizan et al (1971) have recently described 11 cases where clinical signs were localized mainly in cranial nerves but they did not report optic neuritis as a manifestation of Guillain Barre

In multiple sclerosis the early symptoms of the disease often appear as retro bulbar neuritis, (Bradley & Whitty 1968 Kurzke 1968) on the other hand it seems to be extremely exceptional that GBS manifests itself as optic neuritis (Walsh & Hoyt 1969) It is known that some postvaccinal and postinfectious complications may have myelitis and retrobulbar neuritis as late manifestations of neuroallergy Autoimmunization and lymphocytes have been suggested as explanations for demyelination and as a matter of fact sensitized lymphocytes do seem to participate in the pathogenesis of GBS and multiple sclerosis (MS)

In the present communication we shall report a case which showed retro bulbar neuritis as an early symptom of GBS Special attention is paid to the role of immunological aspects in the development and treatment of our case and comparison is made with retrobulbar neuritis appearing in MS

Case report

A 62 year old farmer was admitted to the Department of Ophthalmology because of abrupt loss of vision in the right eye He had complained of pains in his shoulders for two weeks and was having headaches Under detailed ophthalmological examination the following findings were recorded R E V = Hand moving L E V = 6/6 There was an absolute scotoma in the central and temporal field of vision O D the field of vision was normal O S The pupils were of equal size but the right eye reacted sluggeshly to light Slit lamp examination tension and ophthalmoscopy were normal in both eyes The position and direction of the eyes were normal

The common laboratory tests were normal X ray examination of skull and cervical vertebrae and tonography examination of chiasm were also normal EEG and clinical neurological examination showed no pathological findings Virus antibodies against influenza A and B parainfluenza I parotitis measles cytomegalo and herpes were determined (in the Department of Virology University of Turku) in the serum of this patient taken during the acute phase and 2 and 8 weeks later No significant increases in the complement fixing antibody titres were observed

The patient was diagnosed as having retrobulbar neuritis and was treated with cor tisone (Dexamethasone) for 3 weeks Already during the first days of treatment the retrobulbar neuritis began to improve and after 12 days the vision was 6/6 in the right eye and the perimetry was quite normal as well as O D The patient left the hospital in good condition

After the first week at home he noticed weakness in his right leg and unsteadiness in walking Because the progression of these symptoms continued the patient was ad mitted to the Department of Neurology Under neurological examination the following

abnormalities were found slight dysmetria positive Romberg extensor plantar reflex on the right side decrease of muscle power and slightly decreased senses of touch pain, temperature and vibration below the level of Th X–XI In order to verify the diagnosis the following examinations were performed 1) Whole column X ray examination show d multiple degeneration of disci intervertebrales and pelvic bones thorax examination, long bones and oxygen myelography all gave normal results 2) Liver kidney and blood glucose fasting tests were all normal 3) Brain scan was normal but EEG examination showed some diffuse abnormalities which were not apparent in the first EEG 4) Lumbar puncture showed an increase of proteins from 670 mg/l to 1460 mg/l in three successive examinations no increase of cells were found in CSF Cellulose acetate electrophorese of CSF showed increased values for y globulins IgG content of CSF increased in successive examinations from 4 5 to 12 % and a slight left side paralysis in mastix was found 5) IgM content of serum was taken twice and values were 4900 and 4600 mg/l IgA and IgG content of serum were normal 6) Electromyographic examination was repeated three times and changes typical of GBS were found.

The whole clinical picture showed features fitting GBS Because the clinical symptoms progressed rapidly and the patient could no longer walk or stand it was decided to begin ACTH treatment and rehabilitation. Within a week after treatment muscle strength improved and the patient could stand and begin more extensive physiotherapy ACTH was continued for 4 weeks

The patient was seen afterwards at the out patient department and was treated with steroids because the disease showed relapses which were verified by electromyographic examination No signs were found later to suggest the involvement of optic nerves

Discussion

Our case showed some unique features the most striking being that retrobulbar neuritis was the first clinical manifestation of a disease entity which later showed features of myelitis (extensor reflex sensory level reduced muscular strength which turned into flaccid paralysis and loss of tendon reflexes) Gradually the clinical picture progressed manifesting itself as GBS in accordance with many well accepted criteria (Poser 1969) The response to treatment with ACTH was also typical As far as we know there are no other cases of GBS which have shown retrobulbar neuritis as the first clinical sign of the disease

As is usual in half of GBS cases we could not demonstrate any preceding infection to be the cause of the disease (Ravn 1967) All virus antibody titres tested were also within normal limits Elizan et al (1971) recently pointed out that GBS can be limited also to cranial nerves but they did not comment on retrobulbar neuritis In our case the development of GBS after retrobulbar neuritis was rather unusual at first in that it showed features of myelitis as a transitional sign and only later developed into GBS

Although virus infection can trigger off the disease and may also be necessary for the development of tissue lesions we have in our case findings which demonstrate clearly the abnormalities in immunoglobulins without changes in viral antibodies CSF showed normal IgG content at first but then the level increased In addition IgM globulins of serum which contain demyelinating antibodies as well as other immunoglobulins showed four times increased values Both these findings together with the slight abnormality in mastix precipitation reaction demonstrate that pathological immunoglobulin production was associated with the progression of clinical disease

If immunopathogenesis explains the various developments observed two alternatives can be supposed First one may assume that if the sensitization of lymphocytes is the decisive factor this development has been directed towards antigenic protein of the central nervous system and peripheral nerve myelin Such a phenomenon can in fact happen as Caspary & Field (1970) have shown The second possibility is that demyelinating antibodies (possibly in IgM globulin fraction) are destructive to both central and peripheral nerve myelin This possibility has been raised by Cook et al (1971)

As far as multiple sclerosis is concerned it is a well known fact that in most cases the optic nerves are affected (Cartner 1953) This may be due to the close association between optic nerves and CSF or vascularization Both of these aspects seem to be characteristic for the development of early symptoms of MS The other possibility for explaining the susceptibility of optic nerves to MS and related diseases is the high content of antigenic protein (Mehl & Wolfgram 1969)

Our case showed clearly that steroid and ACTH are advantageous in the treatment although many question their value in retrobulbar neuritis MS and GBS It is difficult to know how long to continue the steroid or ACTH treatment in order to avoid relapses as Asbury et al (1969) have shown that in spite of silence the transformed lymphocytes can be found around venules in nerves years after the major symptoms of GBS have disappeared Although the role of neuroallergy in the development of these disease entities is referred to in many instances and treatment is aimed towards suppressing inflammatory and immunological reactions our knowledge of the exact pathogenesis is still incomplete

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From the Ophthalmic Department of the University Hospital, Turku Finland (Head Prof Arvo Oksala)

EXPERIMENTAL OBSERVATIONS ON THE ACOUSTIC SHADOWS CAUSED BY SOME PATHOLOGICAL CONDITIONS ON THE ECHOGRAM OF THE SCLERA

BY

ARVO OKSALA and SIRKKA LIISA JAASLAHTI

In this experimental investigation a scleral rear wall calotte of a pig eye acted as the tissue in which the acoustic shadow showed up The amount of attenuation was assessed by measuring the echo amplitudes in A scan A foreign body and tumor tissues produced a strong acoustic shadow while the shadow from coagulated blood was smaller The smallest at tenuation of ultrasound was caused by uncoagulated blood Clinical ultra sonic diagnosis presently utilizes the acoustic shadow on the rear eye wall produced by an intraocular foreign body or a fairly large choroidal melanoma

Key words acoustic shadow – echogram sclera

In the ultrasonic diagnosis of intraocular melanomas investigators have for a long time taken advantage of the clinical observation that the rear eye wall echoes which are reflected from behind choroidal melanomas with diameters of at least 5 mm are distinctly lower than normal echoes (Oksala 1959 Prei sova & Vanysek *1965) Nover & Glanschneider (1965) showed experimentally* that the attenuation of ultrasound in both the human lens and a melanoma is approximately of the same order

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At a perpendicular examination the sclera of a live human eye emits 2 almost equally high echo peaks which have also been used for the standardization of clinical examinations (Oksala 1968 1971 Ossoinig 1971) In these cases the examination is begun by using such amplification as is needed for obtaining 1–2 mm high echoes from the sclera Depending on the object of the examination the amplification of the equipment is then increased by an appropriate amount of decibels

The attenuation of ultrasound caused by *intraocular pathological conditions* is best observed in the changes that they produce on the rear eye wall echograms in both A and B scan examinations In an A scan examination the effect of relative shadows can be measured accurately from the amplitudes of the scleral echoes but an absolute shadow causes a complete disappearance of scleral echoes In a B scan examination a relative shadow is by no means equally exactly measurable and it may even show up as an empty space in the rear wall echogram An absolute shadow is always discernible in the form of an opening in the rear wall echogram

This paper is based on experimental studies with both A and B scans of the acoustic shadows on the scleral echogram caused by various pathological conditions a foreign body uncoagulated and coagulated blood and a tumor

Material and Methods

The equipment used for this investigation was Kretztechnik s ultrasonic equipment model 7100 MA With this equipment it is possible to obtain simultaneous A and B scan pictures of the object The frequency of the transducer was 8 MHz and the diameter 5 mm In B scan examination the movement of the transducer was linear The examination was made in a bowl of water in which the transducer was *immersed* *The tissues to be examined* were placed on a copper wire stand in the same bowl of water

A scleral rear wall calotte was prepared from the eye of a newly slaughtered pig The foreign body used was a lead ball with a diameter of 3 mm Coagulated and uncoagulated blood came from the patients uncoagulated blood being citrate blood The tumors used were 7 myoma uteri and 3 carcinoma mammae tissues which were cut into pieces 10 × 5 × 5 mm

The acoustic shadows caused by a foreign body uncoagulated and coagulated blood and tumors in the scleral echograms were investigated by A and B scans The foreign body was placed on the bottom of the calotte the calotte was filled with uncoagulated or coagulated blood but when the effect of a

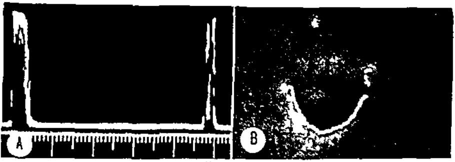


Fig 1
A shows an A scan echogram of the sclera and B a B scan echogram of a scleral rear wall calotte

tumor was examined the tumor was placed either on the bottom of the calotte or on its sides The distance of the transducer from the bottom of the calotte was ca 45 mm In A-scan examination the sound beam was always directed as perpendicular as possible to the calotte A-scan was used for measuring the echo amplitudes Every situation was repeated at 10 different times and 2/0 photos were taken of the echograms

Results

The investigation of the pictures showed that the results of the various situations were very coherent and easily repeatable The results will now be given in the form of some echograms and measurements

Scleral echograms

Figures 1 A and B present echograms obtained in A and B scan examinations In the A scan picture one can see 2 almost equally high adjacent echoes reflected by both surfaces of the sclera In the B scan picture the echogram resembles the shape of the rear wall calotte that was used

The effect of a foreign body on the echogram of a scleral calotte

The 2 high and narrow echoes on the right in Fig 2 A are reflected by the foreign body i e both surfaces of the lead ball The lead ball produces a relative shadow so strong that the 2 echo peaks of the sclera are reduced to 1 low echo as shown by the arrow In the B scan picture (Fig 2 B) the echo reflected

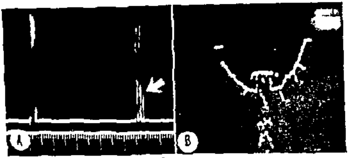


Fig 2

A shows an A scan echogram of a lead ball and of the sclera The 2 echoes reflected by the lead ball are high and narrow The arrow points to the low echo from the sclera In B one can see a B scan echogram in which the lead ball is represented by a line of light points

by the lead ball looks like a line This is due to the diameter of the transducer and its movements The B scan picture gives the impression that the lead ball produces an absolute acoustic shadow in the scleral echogram The reduction in the rear wall echo caused by the foreign body was 6–12 db measured from A scan pictures

The effect of uncoagulated blood on the scleral echograms

Fig 3 was taken after uncoagulated blood had stayed in the calotte for ca 10 minutes On the right in Fig 3 A one can see high echoes reflected by the

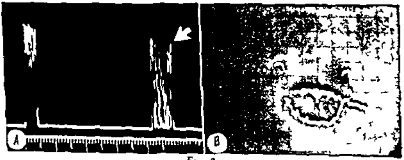


Fig 3

A shows an A scan echogram from a case where the scleral rear wall calotte was filled with citrate blood The scleral echoes are marked by an arrow B shows the same situation in B scan

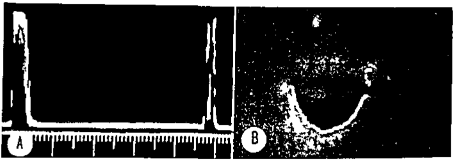


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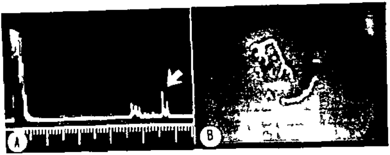


Fig 5
A shows an A scan echogram of a case where a piece of myoma uteri tissue is placed on the bottom of the scleral calotte The scleral echoes are marked by an arrow B shows a B scan echogram of a case where the myoma uteri tissue was placed on one side of the calotte

A scan On the right one can first see low echoes reflected by the tumor and further right 2 clearly lowered echoes from the sclera (arrow) In B scan a typical result was the disintegrating effect of the tumor on the scleral echo gram Fig 5 B shows a typical observation In this case the tumor was placed on the side of the calotte and the sclera behind it reflects only some light points The measurements made in A scan showed that tumor tissues lowered the scleral echoes by 6–12 db depending on the position of the tumor in the calotte In B scan it was impossible to determine whether the shadows that appeared were relative or absolute

Discussion

The results showed that some intraocular pathological conditions often produce distinct shadows in scleral echograms The shadow caused by a foreign body is quite strong and may be almost absolute In B scan it will appear as an acoustically vacuous area in the rear wall echogram In clinical work this phenomenon has already been used to find and localize foreign bodies near the rear eye wall

Uncoagulated blood in the vitreous humor seems to have only slight effect on the scleral echoes that were investigated in A and B scan examinations Coagulated blood however attenuates ultrasound more than uncoagulated blood and produces clearer acoustic shadows This phenomenon can be used clinically to distinguish vitreous humor exudation and uncoagulated blood from a blood coagulum If the vitreous humor is filled with a large blood

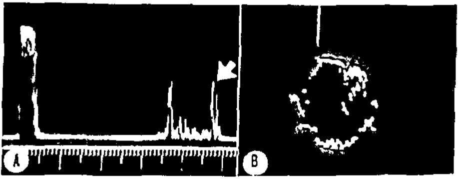


Fig 4

A shows an A scan echogram from a case where a blood coagulum filled the scleral rear wall calotte The scleral echoes are marked by an arrow B shows the same situation in B scan

rear eye wall (arrow) The echogram of the calotte in the B scan picture is almost complete and closely resembles the echogram obtained in the control examination i e in water (Fig 3 B) Citrate blood caused only a slight lowering by 1–2 db in the rear wall echoes

The effect of coagulated blood on the scleral echograms

Fig 4 A represents the result obtained in A scan On the right one can see first a higher echo from the surface of the blood coagulum followed by low echoes from the coagulum The echoes most to the right are the 2 distinctly attenuated echo peaks of the sclera (arrow) In B scan (Fig 4 B) the surface and anterior parts of the coagulum reflected several echoes while the interior parts of the coagulum were pictured as acoustically empty areas Every now and then the calotte was seen as a continuous light line but if so desired the echogram of the calotte could be made quite discontinuous by shifting the coagulum slightly A scan examinations showed that coagulated blood produces a fairly strong relative acoustic shadow on the rear wall and lowers the scleral echoes by 4–6 db at a perpendicular examination In B scan which is clearly less sensitive than A scan the scleral echogram contained vacuous areas but it was impossible to determine whether they were relative or absolute shadows

The effect of a tumor on the scleral echograms

Myoma uteri and carcinoma mammae tissues both produced similar results Fig 5 A represents the lowering effect of myoma uteri on scleral echoes in

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Birth Defects The Second Conference on the Clinical Delineation of Birth Defects Vol III No 3 March 1971 (EYE) edited by D Bergsma. Williams & Wilkins Co Baltimore Price $11 00

This book is dedicated to Frank B Walsh the father of neuroophthalmology It is a report of a conference held at the Johns Hopkins Hospital May 26–31 1969 Richly illustrated and attractively put together the book contains thirteen chapters on various birth defects of the eye Corneal dystrophies and retinal disturbances are of course the main subjects Names of distinguished authors from both sides of the Atlantic can be found

It is natural in a Scandinavian journal to mention Forsius and co workers who are responsible for Dystrofia retinae Dysacusis Syndrome X chromosomal Retinoschisis and Grouped Pigments of the Retina as well as Mette Warburg who has written the chapters on Norries disease and microphthalmus

Holger Ehlers

Dubois *Poulsen A Lairy G C Redmond A (eds)* La fonction du regard (Colloques de l Institut National de la Sante et de la Recherche Médicale) 494 pages INSERM 1971 FF 85 00

This book publishes papers read at a 1969 symposium which present a purely biomedical as well as a psychological ethnographical and cultural approach to the topic

Part I deals with the fixation mechanisms with special emphasis on the afferent path i e various visual stimuli and the vestibular reflexes One simple experiment was especially impressive – the simultaneous recording of a person s eye tracking his own hand performing a sinusoidal movement – which gives evidence of a *feed forward* coord nation.

Part II contains several observations on visual search strategy when looking at pictures of more or less regular patterns together with EEG studies in retinal suppression and rivalry Disturbances of gaze in organic brain lesions are thoroughly considered A truly appalling cas history demonstrates the potential danger to mental integrity in a late restoration of the v sual function in persons born blind or blinded early

Part III covers some of the culture historical borderlands of the general topic If the Freudian aspects of the gaze should happen to have been forgotten in daily practice they can be brushed up here as well as how to use an evil eye

The book provides an easy synthesis of some of the last few years advances in the physiology of gaze The eloborate discussions following nearly every chapter *complete* their top cs in a very informative way

Erik Krogh

coagulum the eye wall may be represented by a discontinuous scleral echogram in B scan

The attenuation of ultrasound caused by tumor tissues was greater than that caused by coagulated blood In clinical work it is however impossible with present equipment to distinguish a tumor e g a melanoma from coagulated blood on this basis alone This is due to the fact that the difference in the amount of attenuation in these two cases is not large enough particularly when we bear in mind that the height of the pathological area under examination is usually only some millimeters On the other hand the difference in the attenuating effect between subretinal fluid and a melanoma is so large that it can be used as a criterion in differential diagnosis if the height of the tumor is at least 5 mm and the frequency ≧ 10 MHz

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Birth Defects The Second Conference on the Clinical Delineation of Birth Defects Vol III No 3 March 1971 (EYE) edited by D Bergsma. Williams & Wilkins Co Baltimore Price $17 00

This book is dedicated to Frank B Walsh the father of neuroophthalmology It is a report of a conference held at the Johns Hopkins Hospital May 26–31 1969 Richly illustrated and attractively put together the book contains thirteen chapters on various birth defects of the eye Corneal dystrophies and retinal disturbances are of course the main subjects Names of distinguished authors from both sides of the Atlantic can be found

It is natural in a Scandinavian journal to mention Forsius and co workers who are responsible for Dystrofia retinae Dysacusis Syndrome X chromosomal Retinoschisis and Grouped Pigments of the Retina as well as Mette Warburg who has written the chapters on Norries disease and microphthalmus

Holger Ehlers

Dubois Poulsen A Lairy G C Redmond A (eds) La fonction du regard (*Colloques de l Institut National de la Sante et de la Recherche Medicale*) 494 pages INSERM 1971 FF 85 00

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Erik Krogh

D R Manley (ed) Symposium on Horizontal Ocular Deviations C. V Mosby Co St Louis 1971 235 pp

Two symposia held 1968 and 1969 at the Wills Eye Hospital in Philadelphia are presented in this book which contains contributions of fifteen North American ophthalmologists with great experience in the field of strabismus

Some sections especially Part I on esodeviations (116 pp) are useful partly as clearly written basic introductions and partly as reviews of present concepts in esodeviations Thus light is thrown on the monofixation syndrome (other synonymes fixation disparity microtropia ect) and on the spectrum of examination methods to mention just a few of the subjects

The importance of evaluating the AC/A ratio prior to any treatment is stressed in exo as well as in esodeviations An earlier published practical AC/C nomogram is presented again

Part II on exodeviations (106 pp) reflects the complexity of this group of disorders which has not always been given in the literature the attention it merits Different materials are presented principles for correctional surgery vary sometimes more than the final results do Some degree of initial esodeviation after surgery for divergent strabismus should – according to some of the authors – be regarded as *propitious*

The final 20 pages on exodeviations are devoted to a panel discussion which furnishes supplemental details and facettes

A relation of the contents to classic and recent works from other authors and schools is lacking only a minimal number of references are given For example it would be impossible to state the origin of a graph (p 147) on the frequency of the occurrence of esotropia and exotropia with their respective refractive errors which is included to illustrate that it is a Common misconception that myopia is more common among exotropes

On the whole however the book is an excellent example of how to present a symposium material didactically and a broad index makes it useful as a handbook too It is recommended as a *stimulus for those who desire more knowledge about* and better results for their strabismic patients

H Fledelius

Kruger Karl Ernst & Manfred Tost Augenarztlicher Untersuchungskurs (Course in Ophthalmological Examination) VEB Georg Thieme Leipzig 1971 156 pages 88 figures Price DM 11

This book is written primarily for the medical student adapted as it is to the demands of the new East German graduate medical education It is remarkly well organized and precisely presented *The many figures are well chosen and informative* It can be recommended for the medical student and for teachers involved with educational curricula

P Brændstrup

Alfred Huber Eye Symptoms in Brain Tumours 2nd ed C V Mosby Co St Louis 1971 3/6 pages 200 figures Translated by F C. Blodi Price $ 32.50

Since its first appearance in German in 1956 Huber s monography has been a classic in neuro ophthalmology This second edition ten years after the first English translation (1961) has been revised and trimmed by the skilled Dr F C. Blodi Half of the text comprises the investigations and the newly introduced fluorescin angiography is recommended for differential diagnosis of choked disc The other half of the book gives in a systematic and topographical way a review of the various eye signs and symptoms in brain tumors according to their site Of special value here is the chiasma syndrome and the differential diagnosis Advanced neuro radiology including scanning and echography can localize about 80 to 90 per cent of the brain tumors but to localize tumors situated at the base of the skull neuro ophthalmology seems to be of the greatest value The clinical material from the neurosurgical department in Zurich comprises about 2 000 cases The incidence of metastatic tumors is low because the material is from the years before cancer of the lungs increased rapidly Today th incidence of metastatic tumors in the brain is about 50 per cent The new edition of Huber s instructive monography will be welcomed by ophthalmologists neurologists and neurosurgeons alike It is a handy book giving you the know how straight from the horse s mouth

Erik Godtfredsen

Magda Radnot & Ágnes Kenyeres Joseph Imre Jr Akadémiae Kiadó Budapest 1971 0 pages 35 figures Price $ 2 40

A most devoted biography of Joseph Imre Jr (1884–1945) has been published by his former pupil Magda Radnot and by Ágnes Kenyeres Imre s origin was academic his education well planned and his career culminated with the highest ophthalmological position in Hungary

Among colleagues outs de Hungary Imre Jr is best known as the talented and artistic ophthalmic surgeon with special expertice in blepharoplasties and corneaplasty But he had widespread knowledge and interest in all fields of ophthalmology including endocrine disorders with ocular man festations

We get a richly facetted description of an outstanding colleague s personality and life his appearance and conduct some intrigues of his career and the burdens that he too had to carry H s success was founded on intell gence industry persistence and humanity

P Brændstrup

Ostlund Kurt Kontaktlinseteknik Fotoprint Kungsbacka Sverige 1971 S Kr 38 00 (Can be purchased from the author Koppavagen 51B 79100 Falun Sweden)

For a long time now there has been need for a Scandinavian textbook on contact lenses Just su h a book has now been published in Swedish it is written by a contact lens optic n and is based on a clear understanding of the ophthal nological aspects of the subject.

The book in question is a concise photo reproduced treatise with more than 100 instructive illustrations Unfortunately however the illustrations do not always follow in the same order as the text

The subject matter is well formulated In some places it is perhaps a little difficult for the beginner reading it for the first time but it is excellent as a compendium for both the prospective ophthalmologist and the contact lens technician

The book covers indications for and against contact lenses adjustment with the trial lens technique and fluorescein patterns Other methods of adjustment for example using a topogometer, are not discussed

There are chapters on anatomy physiology aphakia keratoconus fluorescein coloring of the cornea patients complaints instructing the patient various types of contact lenses and a general survey of instruments solutions etc

It concludes with a list of the medical expressions used in the book (for use of opticians) and a list of the contact lens nomenclature adopted by the Swedish Association for Contact Lens Technique

This book can be recommended as an excellent easily read supplement to larger textbooks

M S Norn

George J Hill Leprosy in five young men Colorado Associated University Press Boulder Colorado *1971 204* pages *90* illustrations *Price $ 8 00*

Five young Mexican males with newly diagnosed untreated leprosy were studied for periods of three to nine months at the Clinical Center National Institutes of Health Bethesda Maryland

The studies comprised the following areas 1) Skin and neuromuscular 2) bacteriology and pathology 3) immunology 4) ophthalmology 5) hepatology 6) gastrointestinal and 7) adrenal – genito – urinary

Even in these newly – diagnosed cases leprosy appeared to be a multi – system disease Mycobacterium lepræ organisms were recovered in sputum gastric aspirate skin ulcerations breast discharge jejunum liver – and renal biopsies prostate and semen peripheral blood and the conjunctiva in great variability among the patients All had genito urinary affections

All five patients had significant ophthalmological problems One patient showed bacilli in his conjunctival scrapings one had diminished corneal sensation and the other three demonstrated impaired motion of the eyelids Alopecia of the eyelashes and eyebrows occurred Chronic and healed chorioretinitis in two patients were probably unrelated to leprosy

Treatment consisted in diaminodiphenyl sulfone diphenyl thiourea and B 663 (a rimizine dye derivative)

It is well known that leprosy is a major cause of blindness in certain areas This study demonstrates clearly that widespread and irreversible tissue destruction has already taken place when leprosy is first suspected Early diagnosis is urgent

P Brændstrup

Massachusetts Eye and Ear Infirmary Retina Service
25th Anniversary Congress September 18 19 20 1972

Distinguished speakers will discuss the development of modern concepts in the areas of – the sensory retina – the vitreous body – methods of examination – pathogenesis and treatment of retinal detachment – developments possible in the future

A social program for ladies visiting historic Boston *Registration fee* $ 100 (Scientific program lunches and anniversary dinner dance) $ 50 (Ladies lunches tours and dinner dance) *Registrar* Charles Regan M D 243 Charles Street Boston MA 02114 *Meetings to be held at* Sheraton Boston Hotel Prudential Plaza Boston MA 02199

The Retina Service Massachusetts Eye and Ear Infirmary

Announces the 10th Annual Course in Retinal Detachment May 18 19 and 20 1972

Subjects to be included Pathogenesis Classification and Differential Diagnosis of Retinal Detachment Surgical Rationale and Techniques Management of Unusual Cases *Surgical* and Postoperative Complications Vitreous Examination Replacement Surgery

Faculty Charles L Schepens M D Ichiro D Okamura M D Robert J Brockhurst M D J Wallace McMeel M D H MacKenzie Freeman M D Ronald C Pruett M D Felipe I Tolentino M D David A Swann M D *Registration* Advance registration required $ 125 for practitioners Residents $ 50 upon application from Department Head Checks to be made payable to Massachusetts Eye and Ear Infirmary

For registration and details – Ronald C Pruett M D Retina Service Massachusetts 0 114

SIDUO V

The 5th Congress of the International Society for Ultrasonic Diagnosis in Ophthalmology (SIDUO V) will be held in Ghent from May 30th to June 2nd 1973 There will be a simultaneous translation from and into English German and French The ophthalmologists who plan to attend the Congress or to give a paper are kindly requested to contact F Goes M D Scientific Secretary of the Congress *Dept of Ultrasonography* Ophthalmological Clinic University of Ghent De Pintelaan, 135 B 9000 Ghent Belgium

Visual Science Information Center

A computer based bibliographic information center covering the world's literature on vision the *Visual Science Information Center* has been established at the University of California Berkeley

Vision literature in books theses reports audio visual materials journals and other serials in several languages is regularly *surveyed* subject indexed in depth and stored in a computer data base *Demand* searches supplying bibliographic citations containing information satisfying *subject questions* are run against the data base in response to

users questions Demand searches may be conducted on a single subject or any combination of subjects using the operatives and or and not Additional search criteria which may be used are author date physical type of publication and language

The data base begins with publications released after November 1970

An author/subject printed index *Vision Index* issued quarterly with annual cumulation is generated from the data base Each quarterly issue contains approximately 2 500 individual citations Annual subscription price $21 00 Volume 1 number 1 March 1971

Occasional bibliographies retrospective to the beginning of the data base and other bibliographic publications regarding vision literature are prepared and distributed Notice of the availability of these publications appears in several sources

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SYMPTOMS AND SIGNS OF INTRACRANIAL ANEURYSMS

With Particular Reference to Retinal Haemorrhage

BY

J A. FAHMY

The clinical symptoms and signs in 154 cases of ruptured intracranial aneurysms are reviewed It is demonstrated that retinal haemorrhage is one of the most important and most common signs (37 4 % – confidence limits 25–40)
It is suggested that fundal haemorrhages be classified on a descriptive basis grade I being mild retinal haemorrhage grade II moderately severe cases of pronounced retinal haemorrhage and grade III severe cases of preretinal or vitreous haemorrhages
A findin of even small retinal haemorrhages in patients who suddenly lose consciousness with or without neck rigidity indicates cerebral an giography

Key words intracranial aneurysms – subarachnoid haemorrhage – retinal haemorrhage – papilloedema – ocular signs

Previously a clinical retrospective study (Fahmy et al 1969) attempted ascertain the aetiology of fundal haemorrhage in subarachnoid bleeding an at the same time to establish the prognostic significance of this finding

Re ved March 10 19 1

The *present investigation* deals with the symptoms and signs and especially the significance of retinal haemorrhage in diagnosing intracranial aneurysms

Material

The material comprises 154 successive patients with ruptured intracranial aneurysms *admitted to the Department of Neurosurgery S Municipal* Hospital Aarhus during the period April 1 1959 to March 31 1967

Among these 154 patients 8 had aneurysms on the anterior cerebral artery 47 on the anterior communicating artery 56 on the internal carotid artery 39 on the middle cerebral artery and 4 on the basilar artery

Seventy nine were females and 75 were males The youngest patient was 9 years old and the oldest 71 *55 %* of the patients were in the age range 40 – 60

Arteriography was performed in 144 cases In 10 it could not be performed *as the patients were too debilitated* and died shortly after admission *In these* cases the diagnosis was confirmed at autopsy

Subarachnoid haemorrhage was verified *in* 142 cases *in* 81 cases by lumbar puncture in 89 cases at operation and in *51* at autopsy

Results

On analysing the various symptoms and signs it was found (Table I) that 117 *patients (76 %)* were *unconscious* whereas 37 had not been unconscious at any time However 2 of them had been somnolent Ninety two patients had been unconscious for less than 24 hours 43 for only a short time Twenty five had been unconscious for more than 24 hours 10 of them for even longer than 48 hours Eighty five patients (55 2 %) exhibited *neck rigidity* In 47 (30 5 %) this sign was definite and marked whereas in 38 (24 7 %) it was mild and in a few cases doubtful *Hemiparesis* was present in 41 patients (26 6 %) 27 patients *(17 5 %) had definite facial palsy* and 10 (6 5 %) were *aphasic*

A total of 64 patients (41 5 %) exhibited one or more *ocular signs* From Table II it may be seen that among the various ocular signs *retinal haemorrhage* was the most common being present in 50 patients (32 4 %) In 21 patients the haemorrhage was bilateral in 29 unilateral There was no definite correlation between unilateral retinal haemorrhage and the side of the aneurysm

Papilloedema was present in 20 patients (12 9 %) in 16 combined with retinal haemorrhage *so that it was only in* 4 *cases that papilloedema* was the only ocular sign In 15 cases the papilloedema was bilateral in 5 cases unilateral

Table I

Incidence of various neurological signs in ruptured intracranial aneurysms

	No of patients	Unconsciou ness	Neck rigidity	Hemiparesis	Facial palsy	Aphasia
Anterior cerebral artery	8	7	6	1	–	–
Anterior communicating artery	47	41	33	11	5	–
Internal carotid artery	56	37	29	15	12	3
Middle cerebral artery	39	29	16	14	10	7
Basilar artery	4	3	1	–	–	–
Total	154	117	85	41	2[illegible]	10

Table II
Incidence of ocular signs in ruptured intracranial aneurysms

	No of patients	Fundal haemorrhage	Papilleodema / Fundal haemorrhage	Paresis of ocular muscles			Visual field defects
				III	IV	VI	
Anterior cerebral artery	8	2	2/–	–	–	1	–
Anterior communicating artery	47	19	7/7	–	–	–	–
Internal carotid artery	56	17	8/6	10	1	–	2
Middle cerebral artery	39	11	3/3	1	–	1	2
Basilar artery	4	1	–	–	–	–	1
Total	154	50	20/16	11	1	2	5

Paresis of eye muscles occurred in 13 patients (8 4 %) 11 having oculomotor paresis 2 abducens paresis and 1 trochlear paresis Only one patient with aneurysm on the internal carotid artery showed a combination of oculomotor and trochlear paresis Oculomotor paresis was found in 10 patients with carotid aneurysm and in one patient with aneurysm on the middle cerebral artery as part of incarceration In 5 cases paresis of ocular muscles was combined with retinal haemorrhage in two cases with papilloedema and in one case with both

Visual field defects appear to be the most uncommon among ocular signs being demonstrable in only 5 (3 2 %) The explanation is that in many patients the general condition did not permit proper perimetry

Discussion

Numerous publications have dealt with intracranial aneurysms from the most diverse aspects but so far no one appears to have emphasized the great diag nostic importance of retinal haemorrhages although this sign is present in almost one third of all patients with ruptured aneurysm Among 136 patients with aneurysms on the anterior communicating artery Krayenbuhl & Yasargil (1959) found papilloedema in 33 retinal haemorrhages in 20 hemiparesis in 16 and aphasia in 11

In the present material retinal haemorrhage proved to be the most common sign after unconsciousness and neck rigidity The retinal haemorrhage occurs almost simultaneously with subarachnoid haemorrhages (Manschot 1944 Walsh & Hoyt 1969) whereas neck rigidity often does not develop until hours after the haemorrhage There may be patients who are deeply unconscious with severe subarachnoid haemorrhage who do not exhibit neck rigidity

As to the shape and site of the retinal haemorrhages there is still some difference of opinion Riddoch & Goulden (1925) found that in most cases the haemorrhages were small and close to the disc Walsh & Hoyt (1969) feel that small haemorrhages are most common but that large preretinal haemorrha ges may occur In their experience vitreous haemorrhage is rare According to Manschot (1944) small haemorrhages may occur but the most typical find ing is large preretinal haemorrhage in the vicinity of the disc Hamby (1952) and Smith et al (1957) found the most characteristic finding to be preretinal subhyaloid haemorrhage

From the present material it is apparent that fundus haemorrhages may range in shape from a single streaked retinal haemorrhage to total blood staining of the vitreous barring any view of the retina

According to the present results it was felt most expedient to classify fundal

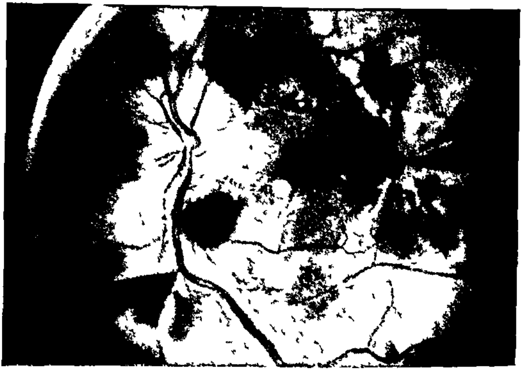


Fig. 1

Fundal haemorrhage grade II–III. Several retinal and preretinal haemorrhages in a 66 year old woman with a ruptured aneurysm on the right carotid artery.



Fig. 2

Fundal haemorrhage grade III. Vitreous haemorrhages in a 66 year old man with ruptured aneurysm on the left internal carotid artery.

Table III

Incidence of fundal bleeding in ruptured intracranial aneurysm (The figures in parentheses indicate vitreous haemorrhages)

	No of patients	Retinal haemorrhages		Preretinal vitreous haemorrhages Grade III	Total
		Mild Grade I	Severe Grade II		
Anterior cerebral artery	8	–	2	–	2
Anterior communicating artery	47	4	9	6/(4)	19
Internal carotid artery	56	7	5	5(4)	17
Middle cerebral artery	39	6	5	–	11
Basilar artery	4	–	–	1(1)	1
Total	154	17	21	12(9)	50

haemorrhages clinically into grades (Table III) Grade I signifies mild retinal haemorrhage i e a few small retinal or papillary haemorrhages grade III severe haemorrhages i e vitreous haemorrhages and large preretinal haemorrhages whereas grade II represents intermediate cases of pronounced retinal and papillary haemorrhages

The grading accounts not only for ophthalmological but also for neurosurgical aspects as the vital prognosis is presumably poorest in patients with severe fundal haemorrhages

Table III shows that the three grades of retinal haemorrhage were in fact equally common and that aneurysms on the anterior communicating artery and on the internal carotid artery cause the most severe haemorrhages (grade III)

The site of the haemorrhages was papillary in 5 cases peripapillary in 22 and diffuse i e peripapillary and peripheral in 33

As to its shape the haemorrhage may be streaked when situated in a layer of nerve fibres and just as often round or flame shaped when situated on the retinal surface or subretinally

Conclusion

From the present findings it may concluded that retinal haemorrhage is one of the most important and most common signs of ruptured intracranial aneurysms occurring in 32 4 % (confidence limits 25–40) A finding of even small retinal haemorrhages in patients who have been in good health and who have then suddenly lost consciousness with or without neck rigidity supports the diagnosis and indicates angiography An early diagnosis may be vitally important and decisive from the prognostic as well as therapeutic point of view

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VITREOUS HAEMORRHAGE IN SUBARACHNOID HAEMORRHAGE – TERSON S SYNDROME

Report of a Case with Macular Degeneration as a Complication

BY

J A FAHMY

A 66 year old man developed bilateral vitreous haemorrhage in connec tion with a ruptured left sided carotid aneurysm The less severe haemor rhage in the left vitreous cleared in 4 weeks without sequelae the profuse right sided haemorrhage not until 7 months later The patient was left with a permanent visual impairment du to macular degenerative changes possibly due to the breakdown products of haemoglobin (iron)
Vitreous haemorrhage in subarachnoid haemorrhage must be more com mon than has been generally assumed

Key words vitreous haemorrhage – subarachnoid haemorrhage – Ter son s syndrome – intracranial aneurysms – macular degeneration

Terson in 1900 was the first to report the occurrence of vitreous haemorrhage (VH) in subarachnoid haemorrhage (SAH) He reported as a new oculocere bral syndrome the case of a man aged 60 who developed in the course of a spontaneous intracranial haemorrhage right sided VH and transient left sided hemiplegia (see Terson 1926)

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Since that time further similar cases have been reported (Doubler & Marlow 1917 Paton 1924 Riddoch & Goulden 1925 Rea 1941 Torres 1964)

Paunoff (1962) reviewing 15 cases from the literature added one of his own In his opinion the syndrome was rare

Castren (1963) who had seen 8 patients with this syndrome between 195? and 1962 expressed the same opinion

Timberlake & Kubik (1952) found that among 280 patients with intracranial aneurysms 66 had retinal haemorrhages Twelve of these patients had VH

Fahmy (1972) demonstrated a similar frequency of VH among patients with intracranial aneurysms finding among 154 such patients 50 with retinal haemorrhages Nine had VH *Aneurysm on the internal carotid artery* was at fault in 4 cases on the anterior communicating artery in 4, and in one case the cause was a ruptured aneurysm on the basilar artery

In the case to be reported below the ophthalmological changes were followed and partly photographed from their onset until the complete absorption of the extravasates 7 months later

Case Report

A 66 year old worker in a glass factory was admitted to the Intensive care Unit shortly after having lost consciousness

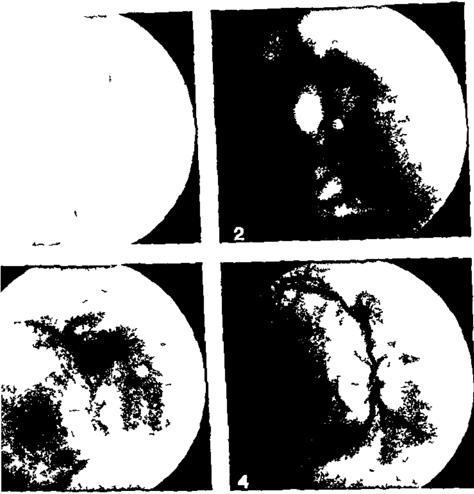
On admission he was somnolent but did not exhibit neck rigidity Shortly after he suffered a right sided brain stem attack and a short lasting right sided hemiparesis When 24 hours later the patient recovered consciousness no neurological abnormalities remained

Lumbar puncture 10 days later showed xanthochromia Left sided carotid angiography revealed a sacculated aneurysm, 1 cm long and 3 cm wide on the left internal carotid artery

The patient was discharged 11 days later feeling fit and without any neurological sequelae He was later referred to the Department of Neurosurgery of Rigshospitalet University of Copenhagen where the diagnosis was confirmed but no indication for operation was found owing to the patient s age and the fact that presumably the aneurysm had bled only once

OPHTHALMOLOGICAL FINDINGS

2½ hours (after the attack) Both discs blurred but not prominent A clear view on the right to the fundus which exhibited several retinal as well as preretinal haemorrhages On the left a blurred view partly because of *synchisis scintillans* and partly because of minor vitreous haemorrhage posteriorly several retinal and preretinal haemorrhages as on the right





Right eye Vitreous haemorrhage in a 6[illegible] year old man with a ruptured aneurysm on the left internal carotid artery

Fig 1 24th day

Fig 2 42nd day

Fig 3 77th day

Fig 4 98th day

Fig 5 [illegible]th month

Diagnosis Fundal haemorrhages as observed in subarachnoid haemorrhage
The patient was seen daily

11th day The right sided preretinal haemorrhage invaded the vitreous almost totally obstructing any view of the fundus

14th day Vision in right eye 3/60 unimproved with glass Vision in left eye 6 60 + 2 00 sph

VH on the right unchanged The retinal haemorrhages on the left in the course of absorption mainly peripherally

28th day VH on the right had changed in colour from dark reddish brown to yellowish grey (Fig 1) VH on the left absorbed The retinal haemorrhages are still in the course of absorption

42nd day VH on the right smaller (Fig 2)

On the left nearly all the retinal haemorrhages have been absorbed only one pre retinal bleeding being left

77th day VH still in the course of absorption (Fig 3) view still blurred *Incipient* minor pigmentations in the macular area On the left all the haemorrhages have been absorbed looking like pigmentations nasally to the disc

98th day VH almost absorbed but still blurred view (Fig 4) Central pigmentations unchanged

7th month Vision in right eye 6/60 + 1 50 sph Vision in left eye > 6/9 + 1 50 sph View on both sides clear pigmentations in right centre unchanged (Fig 5)

Perimetry 3/1000 white and red Central scotoma of a few degrees corresponding to the right sided macular lesion

Discussion

The present case is interesting for several reasons primarily because the most likely ophthalmoscopic diagnosis – SAH – proved correct Mild papilloedema delayed the confirmatory lumbar puncture for 10 days This confirms the author s previous conclusions (Fahmy *1972) that in patients who are otherwise* in good health and suddenly lose consciousness a finding of retinal haemor rhages strongly indicates SAH and a ruptured intracranial aneurysm

Nearly all reported cases of Terson s syndrome in which the cause of the SAH has been located have been due like the present one to a ruptured carotid aneurysm (Doubler & Marlows 1917 Castrén 1963 Torres 1964 Fahmy 1972) or aneurysms on the anterior communicating artery (Fahmy 1972) A common feature of both is the tendency upon rupture to bleed directly into the suba rachnoid space unlike aneurysms of other sites where the bleeding takes place

Table I

Incidence of vitreous haemorrhage in ruptured intracranial aneurysms

Author	Vitreous haemorrhage	Retinal haemorrhage (incl VH)	Aneurysms	Vitreous haemorrhage / Retinal haemorrhage	Confidence limits	Vitreous haemorrhage / Aneurysms	Confidence limits*
Timberlake & Kubik (1952)	12	66	280	18.2 %	10–30	4 %	2– 7
Fahmy (1972)	9	0	154	18 %	9–31	6 %	3–11
Total	21	116	434	18 %	12–28	5 %	3– 8

(P = < 0.50)

partly in the cerebral parenchyma This observation cannot explain the mechanism of VH but indicates a certain correlation between the amount of bleeding which suddenly occurs in the subarachnoid space and the occurrence of vitreous haemorrhage

Some authors believe that Terson s syndrome is rare (Paunoff 1962 Castrén 1964 Walsh & Hoyt 1969) but this cannot be correct as VH makes up 18 % (confidence limits 12–28) of all intraocular haemorrhages in SAH (Table I)

Vitreous haemorrhages rarely develop simultaneously with the SAH but arise probably from ruptured preretinal haemorrhages and do not invade the *vitreous until some days or weeks later*

While a few authors have reported on patients who have regained normal vision following VH (Paton 1924 Walsh & Hoyt 1969) most cases of VH leave permanent impairment of vision either because of persisting opacities (Riddoch & Goulden 1925 Timberlake & Kubik 1952 Castrén 1963 Torres *1964 Walsh & Hoyt 1969)* or because of fibroblastic invasion and *the formation* of connective tissue resulting in retinal detachment (Walsh & Hoyt 1969)

In the present case the cause of the visual impairment in the right eye was a macular change manifesting itself as small dark brownish densely arranged patches of pigment These changes might suggest senile macular degeneration but *this diagnosis has to be rejected* as the patient *had always previously* had good vision in both eyes Another explanation might be that the degeneration had resulted from macular bleedings not accessible ophthalmoscopically during the first period A third possibility is that the macular degenerations were due to toxic action by iron arising after breakdown of haemoglobin in the vitreous

The last mentioned explanation receives support from Regnault s (1970) experimental studies He demonstrated first that the electroretinal response disappears a few hours after injection of blood into the vitreous body of rabbits Later he found microscopic evidence of pyknotic nuclear changes in the retinal rods 5 days and degenerative changes of the pigment epithelium 7 days after injection of haemoglobin into the rabbit vitreous He concluded that haemoglobin was more toxic than whole blood and that the degenerative retinal changes were presumably due to the iron contained in haemoglobin

Castren (1963) treated 3 patients with Terson s syndrome one with ethyl morphine and Priscol locally and obtained a visual improvement from 0 6 to 0 8 but he realized that this improvement might have been spontaneous In the other 2 cases he *successfully exchanged part of the vitreous body (1 5–2 2 ml)* and thereafter obtained almost full visual acuity

This form of treatment could not have benefitted our patient as his visual impairment was not due to a blurred vitreous but rather to a damaged retina

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DEHYDRATION OF THE CRYSTALLINE LENS A POSSIBLE MEANS OF EXTRACTING THE HYPERMATURE CATARACT

BY

A POLZELLA O TIERI and V IURA

Some results of satisfactory operations for the extraction of intumescent cataract lenses after their dehydration with a 50 % solution of glycerol are described The advantages of this technique which facilitates expeditious and optimal seizing of the capsule of the lens are outlined and discussed

When glycerol is brought into direct contact with the crystalline lens dehydration of the lens ensues accompanied by shrivelling of the lens capsule This phenomenon was demonstrated by Vass & Katona (1966) in rabbits after substitution of the aqueous humour with either pure glycerol or glycerol in 50 % dilution These Hungarian authors established from their experience that glycerol does no harm to the intrinsic tissues of the eye and found a transitory shrivelling of Descemet s membrane in only three of the ten animals upon substitution of the aqueous humour with pure glycerol No demonstrable pathological changes were observable upon subsequent histologic examination

As a result of their experiments these authors suggested using 50 % glycerol for cataract surgery when the lens capsule is tightly stretched and cannot easily be picked up with capsular forceps In this communication we describe the results we achieved using this technique experimentally on some of our patients

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Material and Methods

The procedures used in cataract extraction and the methods used for the corneal section were as follows Local anaesthesia was accomplished by injections of 2% Novocaine (procaine) + 0 1% Corbasil (corbadrine) (retrobulbar injection and local akinesia) together with instillations of 0 4% Novesina (oxybuprocaine) The corneal section was made with a Graefe knife after the placement of one corneo scleral suture A basal or sector iridectomy was then performed and a few drops of 50% glycerol solution which had been sterilized by boiling were instilled into the anterior chamber *After waiting for 5 minutes* the crystalline lens was extracted with Arruga s intracapsular forceps and eight further corneo scleral sutures were inserted in the usual manner

Case 1 CA male 65 years old Right eye an intumescent cataract A satisfactory intracapsular extraction of the cataract was easily performed At the end of the operation the anterior chamber was re formed with acetylcholine solution Post operative course after one day marked conjunctival hyperaemia was observed with slight oedema of the peripheral parts of the cornea A certain amount of creasing was apparent in Descemet s membrane The aqueous humour appeared opalescent and on *the sloping parts of the anterior chamber there was a layer of exudate* The pupil was miotic and the pupillary aperture was covered by a layer of exudate mixed with blood

Antibiotic and anti inflammatory drugs were given to the patient locally and generally and mydriatics were locally instilled On the next day the cornea appeared to be considerably clearer and the exudation into the anterior chamber was reduced but the pupil still remained in a state of miosis and exudate was still present in the pupillary area On the third day however the situation had improved considerably The aqueous was limpi l and the pupil was moderately dilated and on the fourth day the eye had settled down and was in a quiescent state

Case 2 F M female years old Left eye hypermature cataract The technique for the oper t on was the same as that used for Case 1 Again after one day there was slight conjunctival hyperaemia the aqueous was sl ghtly cloudy and the pupil was miotic an l covered with a layer of exudate Local and general treatment similar to that gi en to the first case was again used

On the second day after the operation the cond tion of the eye was practically un *changed but* on the third day the aqueous was limpid the pupil was dilated and the exudate had disappeared

Ca e 3 L M male 6 years old Right eye an intumescent cataract Successful anti gl ucomat us sector iridectomy was performed the intumescent *lens be ng extracted* fr m at ove using Lindner s technique acetylcholine was not injected into the *anterior* ham b r at the end of the operation

The postoperative course was excellent no untoward repercussions resulted from the iri lectom y

Case 4 V I female 65 years old Left eye an intumescent cataract Intracapsular extraction of the lens after a sector iridectomy acetylcholine was not injected into the anterior chamber at the end of the operation As in the case of patient No 3 the postoperative course was quite smooth without complications

Case 5 M D E male 58 years old Right eye an intumescent cataract a basal iridectomy was thought necessary and at the end of this operation a mydriatic (collyrium 0 50 % scopolamine) was instilled The postoperative progress was excellent

Discussion

These tentative trial operations that we performed using this new method show that dehydration of an intumescent crystalline lens induced by a 50 % solution of glycerol can be very advantageous when one is endeavouring to grasp the lens capsule with intracapsular forceps It is important to emphasize that the glycerol solution must stay in contact with the crystalline lens for at least 5 minutes a lower time seems not to be sufficient to effect the shrivelling of the lens capsule

The eye tissues exhibit a minimally adverse reaction which quickly resolves if a miotic is not used after extraction of the lens If a miotic must be used then anti inflammatory and mydriatic drugs will be needed to assuage the subsequent uveal inflammation which occurs

Postoperative use of mydriatic drugs eliminates any risk of iridial reaction however we are of the opinion that such drugs should always be used immediately after the extraction if dehydration of the crystalline lens by a 50 % solution of glycerol has been employed

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RETINAL BREAKS WITHOUT RETINAL DETACHMENT IN AUTOPSY EYES

BY

Y R BARISHAK and R STEIN

In 211 eyes pertaining to 195 autopsy cases 21 retinal breaks were found in 12 eyes of 11 cases Retinal tears were associated with vitreous adherence while retinal holes were due partly to intraretinal processes and partly also to vitreous traction The choroid underneath the retinal tears showed areas of thinning and atrophy in some of the eyes and was normal in others Chorioretinal adhesions were detected around oral tears and some of the oral and equatorial holes These adhesions as well as solid vitreous covering the peripheral holes may have been the reason for these retinal breaks having remained silent up to the death of the individual The reason why other in this way not protected breaks had not caused detachment neither the macroscopic nor the microscopic study could reveal

Key words retinal breaks – autopsy eyes

From clinical observations (Colyear & Pishel 1965 Halpern 1966 Dumas & Schepens 196 Hyams et al 1969) and from laboratory studies (Teng & Katzin 1951 Adams 1956 Okun 1961 Foos & Allen 1967 Boniuk & Butler 1968 Andersen & Edmund 1966 Foos et al 1969 Spencer et al 1969) it has been

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known for a long time that only in a relative minority are retinal breaks followed by retinal detachment. Since the inauguration of an active preventive treatment of retinal detachment by Meyer Schwickerath, the distinction between harmful retinal breaks leading to detachment and those that remain silent has become more than an academic problem, especially because in some instances prophylactic treatment may be complicated by early or late changes, particularly in the form of a maculopathy. In a nationwide study ophthalmologists in Israel have tried to get information on the prevalence and interrelationship of the various components of the prehole stage and on the detachment/hole ratio in its dependence on size, shape and location of the break in the general population and in special population groups such as in second eyes, aphakia and myopic aphakia (Michaelson et al. 1966; Michaelson & Stein 1969).

In this study an attempt is made to determine the histological characteristics of retinal breaks found in routine examination of post mortem eyes in the hope of finding out the circumstances which were responsible for their remaining silent, taking into consideration that death might have stopped an eventual development of retinal detachment.

Material and Methods

Post mortem eyes sent to the Mitrani Foundation Eye Pathology Laboratory by the Institute of Pathology constituted the material of this study. All these eyes were taken from white males and females of Jewish extraction. The globes were measured, then cut horizontally, the calottes were mounted in rectangular glass containers and the retinae were studied with the slit lamp microscope. Relevant findings were photographed.

A total of 211 eyes pertaining to 125 autopsy cases were studied. In 86 cases both eyes, and in 39 only one eye were available. The age of the cases ranged from stillbirth to 90 years.

Results

Retinal breaks were discovered in 12 eyes of 11 cases. The age distribution of these cases is presented in Table I. In one case breaks were found in both eyes, an oral hole in one eye and 2 equatorial holes and 1 equatorial tear in the other.

Table I

Age distribution of cases with retinal breaks

Age	No of cases	No of eyes	Retinal breaks			
			No of cases	No of eyes	Holes	Tears
Stillbirth	10	19				
0-1	14	22				
1-10	14	23				
11 20	2	4				
21-30	7	11	1	1	1	
31-40	4	8				
41-50	6	9	3	3	2	1
51-60	19	33	1	1	1	
61-70	27	42	4	5	3	2
71-80	20	36	2	2	2	1
81-90	2	4				
Total	125	211	11	12	8	4

One case in the 61-70 age group presented bilateral breaks and also a tear and holes in one of the eyes (S 522 65)

In Table II the percentage of these retinal breaks in the different age groups is listed Breaks were detected in 8 8 % of cases of all ages and in 13 5 % of cases above 40 years of age This incidence is compared with the findings of other authors

Tears

There were 7 retinal tears in 4 eyes 3 eyes had one tear and one eye 4 tears Three were located in the temporal upper quadrant at the equator and 4 in the lower temporal quadrant near the ora serrata Six of them had flaps and one was beside an area of thinned retina and had *no flap* Among those tears with flaps 4 were associated with peripheral cystoid degeneration and located near the ora and 2 other *equatorial tears* presented no other associated features (Fig 1) As for their size 2 tears were 0 5 × 0.5 mm one tear 2 × 2 mm one tear 2 × 0 5 mm and 3 tears were smaller than 0 5 mm

Table II

Incidence of retinal breaks in post mortem eyes

Authors	Total no of cases	No of cases with breaks	Per cent
All ages since birth			
Teng & Katzin (1951)	101	4	4.0
Okun (1961)	250	21	4.8
Boniuk & Butler (1968)	150	13	8.6
Barishak & Stein (1970)	125	11	8.8
All cases above 20 years			
Foos & Allen (1967)	169	31	18.3
Barishak & Stein (1970)	85	11	12.9
All cases above 40 years			
Okun (1961)	170	12	7.0
Barishak & Stein (1970)	74	10	13.5
All cases above 50 years			
Boniuk & Butler (1968)	100	12	12.0
Barishak & Stein (1970)	68	7	9.7

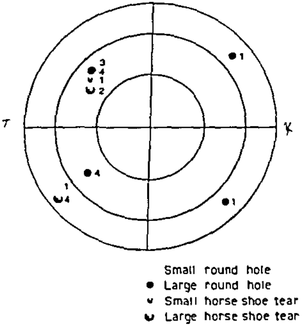


Fig 1

Distribution and type of 21 retinal breaks in 12 autopsy eyes If multiple breaks were present each appears separately The outer circle indicates the peripheral and the middle circle the equatorial zone

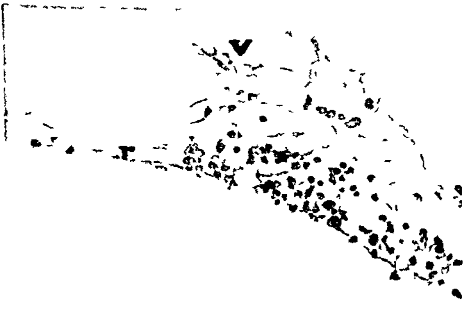
Holes

In 9 eyes 14 holes were discovered 5 eyes presented only one hole 3 eyes 2 holes and 1 eye 3 hole Their distribution and size are illustrated in Fig 1 Two holes were found in an area of lattice degeneration in the upper temporal quadrant of a highly myopic eye with an anterior posterior axis of 27 mm in a 29 year old patient The second eye of this patient was not available Another hole was detected in the vicinity of lattice degeneration inferiorly at the ora serrata in a normal eye of a 49 year old individual Among the remaining holes one was associated with a chorio retinal pigmented lesion 5 with paving stone degeneration 2 with peripheral cystoid degeneration and 3 did not present any associated retinal changes

A posterior vitreous detachment was noted in all the eyes presenting retinal breaks

Histological Characteristics of the Retinal Breaks

Serial sections were performed on all tears and holes



Fig

k rg d pp a ance and atrophy of the peripheral l p of a tear 800 × \ pulling itreous r atroph c retina



Fig 3

Marked rounding up with swinging around of the external granular layer 800 × E external granular layer I internal granular layer n nuclei swinging around the border of the tear

Retinal tears

The most imposing feature among the findings in retinal tears was the presence of vitreous traction This vitreous pull seems to have been responsible for the formation of the flap Retinal pits considered by some authors as the result of vitreous traction and retinal degeneration (Boniuk & Butler 1965) were encountered around the tears Vitreous pulling seems to provoke marked degenerative changes in the area of adhesion The peripheral lip of a tear presented a ragged appearance was thinner than usual and even atrophic (Fig 2) On the other hand the central lip which was not subjected to vitreal traction showed generally a rounding up with a swinging around of nuclei of the external granular layer and fusion of both granular layers (Fig 3)



Fig 4
Chorioretinal adhesion around oral tear 400 × A chorioretinal adhesion

On both sides of a tear rods and cones were usually missing and a moderate atrophy of the inner layers thickening of the vessel walls and occlusion of capillaries were present

Aberrant vitreo retinal adhesions might be responsible for the development of equatorial tears Such adhesions might be due to connections between the hyaloid and retinal vascular system during the embryonal development (Pau 1959)

Chorioretinal adhesions around tears were claimed to be responsible *for* the silence of tears (Okun 1961) We found such adhesions only around oral tears (Fig 4) The choroid showed normal structure and thickness and only moderate hyalinization around such a tear Occasionally a slight lymphocytic infiltration was seen at these sites (Fig 5) At the site of some tears thinning of the choriod was present (Fig 6) in others an almost *complete atrophy* and still in others a normal thickness with a patent choriocapillaris though sometimes hyalinization between the vessels severe enough to involve all layers was the most striking feature (Fig) The distance between such different looking aspects of the same area of the choroid may be not more than 100



Fig 3
Marked rounding up with swinging around of the external granular layer 800 × E external granular layer I internal granular layer n nuclei swinging around the border of the tear

Retinal tears

The most imposing feature among the findings in retinal tears was the presence of vitreous traction This vitreous pull seems to have been responsible for the formation of the flap Retinal pits considered by some authors as the result of vitreous traction and retinal degeneration (Boniuk & Butler 1965) were encountered around the tears Vitreous pulling seems to provoke marked degenerative changes in the area of adhesion The peripheral lip of a tear presented a ragged appearance was thinner than usual and even atrophic (Fig 2) On the other hand the central lip which was not subjected to vitreal traction showed generally a rounding up with a swinging around of nuclei of the external granular layer and fusion of both granular layers (Fig 3)



Fig 7

Choroid with patent choriocapillaris but severe hyalinization at the site of a tear 800 × c patent choriocapillaries h hyalinization.

to 150 microns Similar degenerative changes are observed in the peripheral choroid of old people (Wolter 1959) At the area of tears the pigment epithelium of the retina reacted with formation of drusen

Holes

In the development of retinal holes vitreous traction seems not to be the main causative factor Operculated and not operculated holes are to be distinguished In the development of non operculated holes mostly intraretinal causes are involved In one case the hole appeared in a region of thinned and gliotic retina with liquefied vitreous overlying it Both peripheral and central edges of a hole showed usually rounded borders with swinging around of the nuclei of the external granular layer and fusion of both granular layers At the central edge the walls of the capillaries were thickened (Fig 8) A double hole of another case appeared in an area of lattice degeneration characterized by advanced atrophy of the retina obstruction of vessels and liquefaction of the overlying vitreous

On the other hand vitreous traction seems to play a major role in the



Fig 5

Lymphocytic infiltration in choroid around a tear Plasma cells are also present 800 ×
P plasma cell L lymphocytes p pigment epithelium



Fig 6

Thinning of choroid at the site of a tear 400 × C atrophic choroid

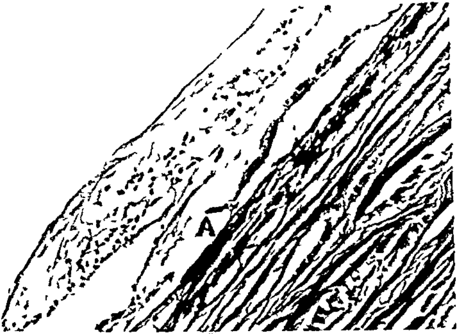


Fig 9
Chorioretinal adhesion around hole (A) 400 × (Copy of color slide)

not led to a retinal detachment The other 3 tears were situated in the equatorial area of the upper temporal retina One was close to an area of thinned atrophic retina in an eye with a sagittal diameter of 24 mm in a 76 year old case The other 2 tears were found in myopic eyes with an anterior posterior axis of 25 and 28 mm respectively in individuals aged 62 and 67 years There were no chorioretinal adhesions surrounding them and the only constant feature was vitreo retinal adhesion and an obvious vitreous pull inferred from the stretched course of the vitreous fibers Though the histological study gave no clue as to why these tears had remained silent up to the time of the death in a living eye we would not have hesitated to regard these tears as dangerous and requiring closure It is the time factor which plays a deciding role between the appearance of a tear and the terminal incident This factor as well as the dynamic forces of a pathologic vitreous permanently revolving and pulling on the retina during life cannot be assessed in a histological preparation of a post mortem eye that is only a momentary reflection of a pathological process that may have been going on for years (Andersen & Edmund 1966)

The histology revealed that holes may develop in consequence of *intraretinal*



Fig 8
Thick walled capillary at the border of retinal hole Both nuclear layers fuse and the nuclei swing around the border 800 × c retinal vessel n nuclei swinging around the border

development of operculated holes provoking cystoid degeneration and even atrophy of the retina exposed to the vitreous pull In one illustrative case the direction of the vitreous traction was perpendicular to the retina and the vitrous was adherent to a retinal tag or a still adherent operculum

Around some holes strong chorioretinal adhesions and around others foci of aggregated lymphocytes were observed There were holes that did not show adhesions at all Below the holes the choroid showed a marked hyalinization and drusen were present in the retinal pigment epithelium

Discussion

Among 7 tears found in our sample 4 were located at the ora serrata in the lower half of the retina and were surrounded by chorioretinal adhesions These circumstances may have been responsible for the fact that these tears had

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processes such as vessel obstructions lattice and cystoid degeneration as well as by traction of an adherent vitreous that probably itself promotes retinal degeneration Choroidal atrophy as found by Michaelson (1956) and interpreted by him as a causative factor in the formation of retinal breaks was not present in our cases Some of the holes of our series were situated near the ora and covered by the base of the solid vitreous This fact may have prevented the development of a detachment Other holes were located more posteriorly at the equator within areas of lattice degeneration Around some of them chorioretinal adhesions were observed which may have averted detachment Otherwise the same arguments concerning temporal and mechanic factors as they were mentioned above can be brought forward to explain the silence of these holes during the life of the deceased

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EOSINOPHILIC GRANULOMA OF THE ORBIT

BY

HANS ERIK HEUER

A report is presented of a 56 year old woman with a history of some months of protrusion of the left eye slight swelling of the upper lid and decreasing vision Preoperative examinations indicated an intracranial destructive process around the left optic foramen and at operation a small tumor was removed Histological examination showed a typical eosinophilic granuloma which is most unusual at that age occurring almost exclusively in children and adolescents

Key words histiocytosis X – tumor of the orbit – eosinophilic granuloma of the orbit

The term "eosinophilic granuloma of bone was introduced by Lichtenstein & Jaffe (1940) Since then the disease has been described as closely related to Hand Schuller Christian s disease and Letterer Siwe s disease (Jaffe & Lichtenstein 1944) Lichtenstein (1953) included the 3 diseases under the name of "Histiocytosis X and that concept has been supported by most later authors (Oberman 1968) However Nyholm (1967) concluded that Letterer Siwe s disease should be regarded as a separate nosological entity whereas eosinophilic granuloma of bone represents a monosymptomatic and early form of the disse

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minated granulomatosis of the Hand Schuller Christian type the two being gathered under the name of Eosinophilic Xanthomatous Granulomatosis"

Eosinophilic granuloma occurs typically in children and adolescents and its localization in the orbit is exceptional

A case is reported below of eosinophilic granuloma of the orbit in a 56 year old patient

Case report

The patient (No G 39991) is a 56 year old woman with a family history of diabetes (father and paternal grandmother) For the last 15 years she had received medical anti hypertensive treatment and for 10 years treatment for myxedema On control admission for myxedema 6 months prior to the present admission a mild diabetes was disc vered demanding no treatment

She was transferred from a local hosp tal on Oct 30 19 0 where she had been admitted because of 4 to 6 months of light pains around the left eye periodically ex tend ng towards the left ear and a rather sudden marked decrease in visual acuity of the left eye of about one month s duration combined with swelling of the left upper lid There was no history of recent trauma or infection.

Objective examination showed a sl ght swelling of the left upper lid and a marked proptosis without deplacement or deviation Hertel measure being 90–94/102 mm Proptosis was irreducible and non pulsatile Palpation of the orb tal margin was nor mal Ocular motility was normal the eye showed no signs of inflammation there was no chemosis id pupil refracting med a and fundus were normal as was corneal sensibility Visual acu ty was reduced to perception of hand movements temporally The right eye was normal

An ear nose and throat examination was non contributory General examination showed no signs of systemic disease like lymphadenopathy hepatosplenomegaly or pulmonary involvement The patient had a hypertensive and arteriosclerotic cardiac disease with no signs of incompensation She was euthyroid and neurological examina t on re ealed n thing abnormal

Blood tests showed ESR 6 mm Hb 16 3 g 100 ml electrolyte values normal WR neg t ve Serum cholesterol was not examined Leucocyte count was 10 3^{9}/ l with 82 per cent ne itroph ls and no eos nophils Blood glucose varied between 133 and 1 4 mg 100 ml

EEG n rmal

Left carot d a teri graphy normal

Scann ng with ^{99m}Technetium (Heuer & Ehlers in press) showed no d fference in a tiv ty betwe n the rb ts

X av of the orbits showed a destruction of the ala parva of the left sphenoid (Fig 1) and tomography showed enla gement of the left optic foramen A skeletal survey sh wed no other destructive changes

During the per od of pre-operative exam nations visual acuity of the left eye im pr d to f nger counting 1 m an l per m try showed a large central scotoma



Fig 1
X ray of the orbits showing a destructive process of the medial part of the left ala parva

At left frontal craniotomy on Dec 7 1970 (by N Ovesen) a tumor the size of a pea was found extradurally just behind and laterally to the entrance of the optic nerve into the orbit The tumor was easily separated from the optic nerve and the underlying eroded bone was removed

Histological examination of the tumor (Fig 2) showed a typical eosinophilic granuloma consisting of mesenchymal cells with round and angular nuclei and well marked light vacuolized cytoplasma The cells lay close together in large sheets and groups surrounded by a brim of lymphocytes and numerous eosinophilic leucocytes The walls of the few vessels present were slightly thickened No signs of malignancy were seen Edema and recent hemorrhages were present (Sign Edith Keske Nielsen)

Postoperatively the patient received radiotherapy a dose of 1500 R being applied with ^{60}Co over 9 days

Later controls have shown persisting slight swelling of the left upper lid and slight proptosis Visual acuity has remained unchanged

Discussion

Eosinophilic granuloma of bone is characterized on X rays by solitary or multiple cystic defects of bone characteristically showing little or no reactive changes of the surrounding bone (François et al 1954 Nyholm 1967) It is

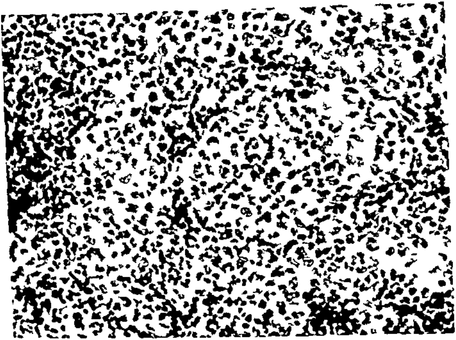


Fig [illegible]

Eosinophilic granuloma of the orbit in a 5[illegible] year old woman The characteristic types of cells are visible Hematoxylin eosin × 160

found in decreasing order of frequency in the skull the pelvis the vertebrae the ribs and the long bone of the limbs Calmettes et al (1966) mention 30 previous reports of eosinophilic granuloma of the orbit the site of predilection being the upper temporal brim Two cases have been described in literature of eosinophilic granuloma involving the soft parts of the orbit only (François et al 1954)

Histologically its main features are large phagocytic histiocytes occasional actively phagocytic multinucleated giant cells and more or less conspicuous numbers of eosinophilic cells especially eosinophilic leukocytes (Jaffe & Lichtenstein 1944 Reese 1963) The histological evolution passes from a phase of histiocytic proliferation to a granuloma formation and from there through a xanthomatous stage to a final stage of cicatricial fibrosis (Layani & Aschkenasy 1951)

The etiology is entirely unknown

Most often no changes of blood lipids can be demonstrated although cases

with hypercholesterolemia have been reported (Gornig 1968) Eosinophilia is a frequent but by no means constant feature

Most authors advocate taking a specimen for histological diagnosis though it is reported that bone defects without surrounding reaction in a child with symptoms of an orbital tumor and eosinophilia are strongly suggestive of eosinophilic granuloma (François et al 1954)

In the present case typical symptoms were present but as eosinophilic granuloma is seen almost exclusively in children and young adults the diagnosis is not likely in a patient of 56 years

The prognosis of the solitary eosinophilic granuloma is usually good almost regardless of the choice of therapy although malignant cases have been reported (Srivastava et al 1968)

At present treatment is surgical excision if possible radiotherapy in doses generally less than 1000 R and corticosteroids or as in our case a combination of these

Healing by resolution is reported even without any therapeutic intervention (Jaffe & Lichtenstein 1944)

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COMPARISON BETWEEN TWO METHODS OF REMOVING THE VITREOUS BODY

BY

MICHAEL BAY

Two methods for removal of the vitreous body are described. The efficacy of the methods is discussed and evaluated by an investigation of ten rabbits with ^{14}C labelled mannitol infused intravenously through an ear vein catheter.
The results show that removal of the vitreous body by means of perscleral puncture is more inaccurate compared to removal by means of enucleation, freezing with liquid nitrogen and dissection. The explanation of the lower applicability of the perscleral puncture method is probably the different distribution of mannitol in the vitreous body after 90 minutes constant plasma concentration. The perscleral puncture is thus only applicable when we are sure that a diffusion balance of the examined compounds is present between the central and the peripheral parts of the vitreous body.

Key words: vitreous – ^{14}C labeled mannitol

In several studies the intrusion of various pharmacological compounds into the vitreous body has been considered, partly because it is of practical clinical interest and partly because examining the conditions of diffusion and distribution into this homogeneous connective tissue may have great theoretical significance.

In contrast to the entirely cellular lens the vitreous body is an almost non

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cellular organ It is the largest amount of inter cellular substance in the organism and at the same time one of the most simply composed connective tissues The vitrous body is a transparent gel with a water content of approximately 99 per cent The dry matter consists mainly of the collagen and hyaluronic acid (Graymore 1970) At the posterior side and peripherally the vitreous body is bounded by membrana limitans interna and at the anterior side by a very thin membrane which is in contact with the lens The distribution of the collagen in the vitreous body is very heterogeneous being most highly concentrated in the anterior part of the vitreous body toward the ciliary body The second highest concentration is found in a layer next to the retina and the lowest concentration is in the centre The amount of collaginous fibres peripherally is so pronounced that it provides a sliding transition to the retinal membrana limitans interna (Adler 1965) The content of hyaluronic acid is likewise largest peripherally (Balazs 1958)

In previous studies on the composition of the vitreous body as well as in studies on the characteristics of the blood/vitreous barrier two principally different methods of removal of the vitreous body have been used

(1) The vitreous body is removed *in toto* after enucleation and deep freezing with liquid nitrogen or carbon dioxide snow and then dissected

(2) The vitreous body is removed by perscleral puncture followed by aspiration

In the great majority of all these studies on the vitreous body removed according to the latter method only a few for instance Davson & Duke Elder 1948 Davson et al 1949 and Bleeker 1968 have used enucleation It is however not possible to evaluate the two methods based on the literature because conditions varied from study to study The purpose of the present study is therefore to evaluate the accuracy of the two methods by which representative specimens of the vitreous body can be obtained

Material and Methods

Ten albino male rabbits weighing from 1800 to 2200 g on an average 2225 g were used *in the study* ^{14}C labeled mannitol with a specific radioactivity of 48 mci mM from Radiochemical Center Amersham was infused intravenously in doses of about 2 μc per kg bodyweight

The animals were divided into two groups A and B

Group A – the vitreous body was removed by means of enucleation deep freezing by dipping into isopentane in liquid nitrogen and careful dissection

Group B – the vitreous body was taken out by means of perscleral puncture followed by aspiration with Acafirm hypodermic needle No 16

The weighing was performed for all removed vitreous bodies by means of a Mettler scale Type HGT

All the rabbits were sacrificed by an air emboli through the ear vein catheter after 90 minutes constant plasma mannitol concentration The plasma concentration was kept constant by means of a suitable initial dose of mannitol followed by a continuous infusion of a maintenance dose through a Polystan catheter (i d 0.28 mm) inserted into the marginal ear vein Mannitol is excreted by a glomerular filtration process which means that clearance is equal to an insulin clearance of about 9 ml/min (Broen Christensen 1965) A rabbit weighing about 2 kg will have an extra cellular volume of 350 ml and an infused mannitol dose will therefore be excreted during approximately 40 min Thus the maintenance dose for 90 min will correspond to the initial dose multiplied

Table 1

Ratio after 90 minutes constant plasma concentration The vitreous body/plasma in experimental groups A and B

Group A			Group B		
vb/plasma		$\frac{\text{right}+\text{left}}{\frac{\text{right}+\text{left}}{2}} \times 100$	vb/plasma		$\frac{\text{right}-\text{left}}{\frac{\text{right}-\text{left}}{2}} \times 100$
Right Left	0.066 0.058	12.9	Right Left	0.050 0.045	10.5
Right Left	0.066 0.069	4.4	Right Left	0.138 0.082	50.9
Right Left	0.048 0.044	8.6	Right Left	0.051 0.037	31.8
Right Left	0.066 0.077	15.3	Right Left	0.030 0.033	9.5
Right Left	0.051 0.046	10.3	Right Left	0.084 0.038	[illegible]

The numbers in the columns vb/plasma indicate the relation between the mannitol contents and plasma for right and left eye The percentual difference of the means from right and left eye is stated in the next columns

Table II

The weight of the vitreous body in experimental groups A and B stated in grams

Group A		Group B	
	Weight (g)		Weight (g)
Right	1 64	Right	0 94
Left	1 69	Left	0 9,
Right	1.5?	Right	0 74
Left	1 45	Left	0 57
Right	1 78	Right	0 88
Left	1 64	Left	0 6?
Right	1 87	Right	1 41
Left	1 94	Left	1 0?
Right	1 88	Right	1 66
Left	1 80	Left	1 41

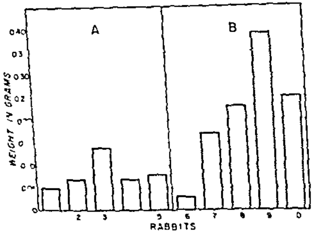


Fig 1

The d fference between mann t l concentration in r ght and left vitreous body after 90 m nutes c nstant pla ma concentrat on in experimental groups A and B

by 2 25 This maintenance dose was applied in all the experiments The plasma concentration was determined every tenth minute and blood tests were taken in the other ear vein by means of phlebotone and 1000 μl Carlsberg pipette Heparin was used as anti coagulation agent The infusion through the ear vein catheter was made with an electrical motor attached to a 20 ml Luer syringe The stable work of the motor was controlled by a revolution indicator

The blood tests were collected in heparin centrifuge glasses about 0 5 in each test and centrifuged immediately after 200 μl of the plasma was removed by a pipette and the protein precipitated with zinc hydroxide (Somogyi 1930) After centrifuging 200 μl of the supernatant was removed by pipette into counting glasses containing 8 ml scintillation fluid (Bray 1960) The radio activity in each test was determined by means of a Pacard Tri Carb liquid scintillation spectrometre model 314 EX by counting for 100 minutes Tests from the vitreous body were treated in the same way as the blood tests with a preceding decomposition of the tissue by hyaluronidase All the counting numbers in the investigation exceeded the background radiation by a ratio of five

Results

The results from Group A where the vitreous body was removed by means of enucleation freezing with liquid nitrogen and dissection as well as the results from Group B where the vitreous body was removed by means of perscleral

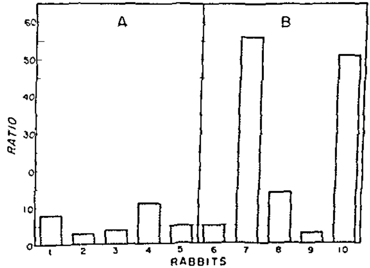


Fig 2

The difference between the weight of the single vitreous bodies from right and left eye in experimental groups A and B

Table III

The mannitol plasma concentration indicated by mean and standard deviation for experimental groups A and B

Group A		Group B	
x	41777	$\bar{x}$	56488
s	5993	s	8068
x	36534	x	50092
s	7684	s	3766
x	73878	x	51061
s	8152	s	5519
x	36664	x	87044
s	3597	s	9311
x	49857	x	60440
s	3615	s	8708

Mean (x) and standard deviation (s) for the mannitol contents of plasma for each single experiment The mean is calculated on the basis of a total of *nine observations during* a 90 minute experiment period The values are calculated on basis of the counting numbers after a 100 minute counting period in 8 ml Bray

puncture are shown in Table I It is seen from this Table that the difference of the ratio of the mannitol contents in the vitreous body and plasma at corresponding values from right to left eye is largest in Group B The difference given as a percentage of the mean from right and left eye varies from 8 6 % to 15 3 % in Group A and from 9 5 % to 87 1 % *in Group B*

Table II shows the weight of the vitreous body from right and left eye respectively in the two study groups given in grams It is seen that also the weight varies more in Group B which indicates incomplete removal Fig 1 and Fig 2 show a graphical representation of the numbers from Tables I and II

In Table III the plasma concentration is stated with *means* and standard deviation for each single investigation

Discussion

The results of the present investigation show that *removal of the vitreous body* by means of perscleral puncture is considerably more *inaccurate* than removal

in toto, as the difference in the ratio of the mannitol contents in the vitreous body and plasma expressed in percentage of the means from right and left eye is about 10 times larger in Group B than in Group A. *The most probable reason* for this is that by perscleral puncture a mixture is obtained between central and varying amounts of peripheral vitreous body. This is the most likely explanation because of the anatomic structure of the vitreous body which has a high concentration of collagen and hyaluronic acid peripherally and a steadily falling concentration toward the centre. Furthermore this structure may explain the fact that a greater weight variation is obtained by aspiration as the viscosity is highest peripherally which makes a total aspiration of the peripheral parts of the vitreous body very difficult. Thus removal of the vitreous body *in toto after enucleation and freezing is preferable because possible gradients* of concentration are insignificant. As shown in Table I a total and uniform removal of the vitreous body is obtained by this method.

At removal by perscleral puncture the accuracy of this method will depend on the time which the chemical compound needs to obtain diffusion balance in the vitreous body. This diffusion balance adjusts itself to varying time intervals depending on the molecular radius, the molecular configuration and possible charging of the single compounds.

Removal of the vitreous body *in toto* after enucleation and freezing furthermore *offers scope to determine the gradients of concentration of the single* compounds in the vitreous body by means of a topographical division into sections. A division into sections elucidates also the mutual placing of the vessel systems, i.e. the chorioidal, retinal and ciliary vessels by the passage of the single compounds or compound groups from the blood circulation to the vitreous body.

Acknowledgments

This investigation was carried out by a grant from The Danish National Association against Rheumatic Diseases, Scandinavian Insulin Foundation and Danish Medical Research Council. I wish to thank Mrs. Anne Persson for excellent technical assistance.

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used (Mitchell 1938 Philipson 1969) In the present work the dose response relation was studied Furthermore it was investigated whether an inhibition of galactose metabolism by ethanol influences the dose response relation

Materials and Methods

Female Wistar rats weighing 100 g were kept on a liquid *ad lib* diet containing 1 0 calories per ml Casein constituted 14 % and fat 26 % of the calories In the control diet the remaining 60 % consisted of glucose and in the galactose diets part of the glucose calories was replaced with galactose and ethanol in the following combinations 40/0 30/0 30/15 30/25 30/30 25/25 20/15 20/20 20/25 20/30 15/15 15/25 and 15/30 Initially each of these groups consisted of four rats All diets contained 1 ml per l of a vitamin mixture (ABCDin®) The animals had free access to a cake consisting of a balanced mixture of minerals (Hegsted 1940) during the whole experiment Their water intake was covered by the liquid diet. Twice a week the eyes were inspected with a lens and focal illumination and they were followed by photography using a hand held fundus camera

After 10 weeks the rats were killed The feeding bottles were removed 1½ hrs before killing The lenses were removed and inspected in a slit lamp on an illuminated background Blood was obtained by puncture of the exposed heart and the galactose concentration was determined enzymatically (Hjelm & Verdier 1970) In 20 control rats and 20 rats receiving 30 % of the calories as galactose adenine nucleotides were determined in the lenses Four rats of each group were killed by a blow on the neck 12 hrs and 2 5 7 and 9 days after start of the feeding schedule The lenses of surviving rats were inspected daily in the ophthalmoscope The eyes of the sacrificed animals were enucleated quickly and immediately transferred to liquid nitrogen

The lenses were removed from the frozen eyes and a pool of 8 lenses were ground to powder in a mortar with liquid nitrogen After homogenization in perchloric acid (3N −14 C) weighing centrifugation and neutralization the adenine nucleotide content was determined enzymatically (Adam 1970)

Results

In the albino rat the iris is transparent (Fig 1 a) The cataract first appeared at the equator as subcortical opacity (Fig 1 b) which gradually grew towards the poles of the lens After a period the subcortical cataract rather abruptly (in

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DOSE DEPENDENCE OF GALACTOSE CATARACT IN THE RAT

BY

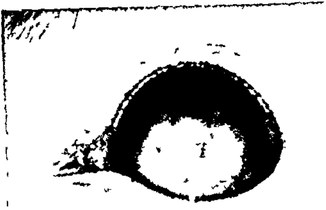
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Feeding of galactose to albino rats results in the development of subcortical and nuclear cataract The time for cataract formation was highly correlated with the dose of galactose the minimum time for development of subcortical cataract being four days and for that of nuclear cataract 45 days
Nuclear cataract did not develop in any case during the 75 days of observation when galactose was given as 15 % of the calories No effect of simultaneous ethanol feeding could be demonstrated
Galactose was found to reduce ATP level of the lens after one week whereas ADP and AMP levels were constant

Key words experimental cataract – dose response – ethanol – galactose – rats

Cataract may be produced experimentally by feeding animals with galactose and certain other carbohydrates (Patterson & Bunting 1962 van Heyningen 1963) When data from different studies are compared it seems that the time required for development of cataract depends on the dose of galactose given (Mitchell 1935) but in most investigations only one dose of galactose has been

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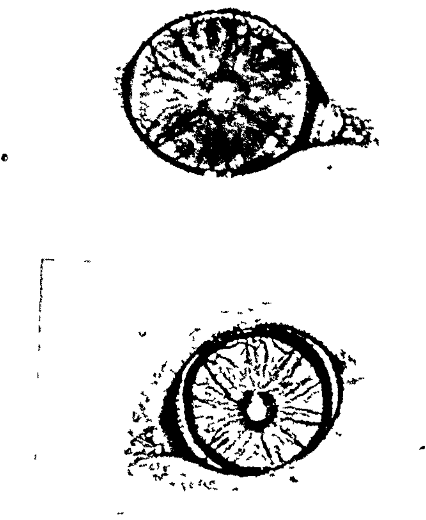
Fig. 1
Ophthalmoscopic appearance of a) normal albino rat b) rat with cortical cataract c) rat with nuclear cataract

Table I
Effect of ethanol on development of galactose cataract

Galactose in diet 30 % of total calories (initially 4 rats in each group*)

Ethanol in diet (% of calories)	0	15	25	30
Appearance of cortical cataract (days)	5	7	5	7
	5	7	7	7
	5	7	9	7
	7	7	9	10
Mean	5.5	7	7.5	7.8
Appearance of nuclear cataract (days)	41	41	45	50
	66	41	66	66
		41	66	
		66		
Mean	54	47	59	58

Five rats died after 11 30 37 71 and 72 days



a

b

the course of less than 24 hrs) developed into a nuclear cataract with the total nucleus of the lens showing a diffuse dense opacity (Fig 1 c) The development of cataract was parallel on both sides The cataractogenic effect is quantitated by the rate of cataract formation i e the reciprocal value of the time (days) required for development of cortical and nuclear cataract Table I shows that the rate of cataract formation is not increased by the amounts of ethanol given in the diet An analysis of the data obtained by other combinations of dietary galactose and ethanol confirms this

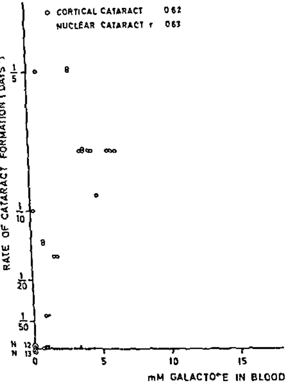
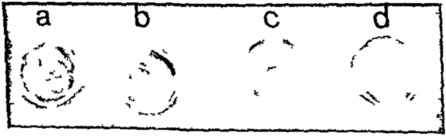


Fig 3

Relation between rate of cataract formation and concentration of galactose in blood.



Fi 4

Appearance of the lens after 5 days of feeding of galactose (% of the calories)
a 0 b 15 c 20 d 30

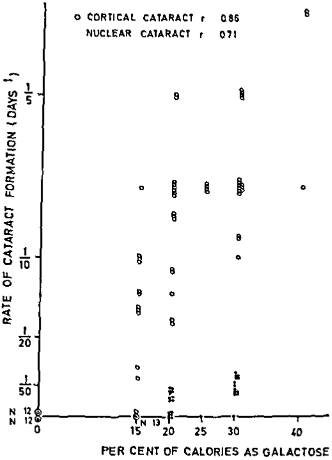


Fig 2

Relation between rate of cataract formation and content of galactose in the diet

Consequently in Fig 2 which shows the rate of formation of cortical and nuclear cataract only the variation in galactose feeding is taken into account It is seen that the rate of cataract formation is highly correlated with the amount of galactose in the diet All rats receiving 15 % of the calories as galactose developed cortical cataract but none of them developed nuclear cataract

Fig 3 shows the relation between the rate of cataract formation and the concentration of galactose in blood at the end of the experiment

Not only the rate of cataract formation but also the degree of cataract after 10 weeks of feeding was found to depend on the amount of galactose given as shown in Fig 4

Fig 5 shows that the concentration of ATP in lenses from rats fed on the 30 % galactose diet decreased on the fifth to seventh day when cortical cataract was observed The concentrations of ADP and AMP were constant

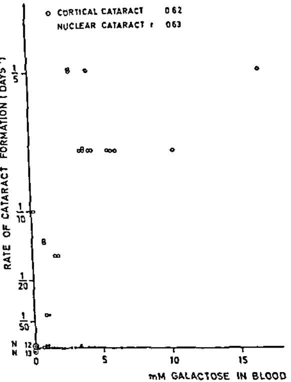


Fig 3

Relation between rate of cataract formation and concentration of galactose in blood

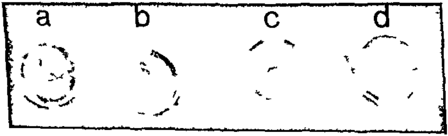


Fig 4

Appearance of the lens after 75 days of feeding of galactose (% of the calories)
a 0 b 15 c 20 d 30

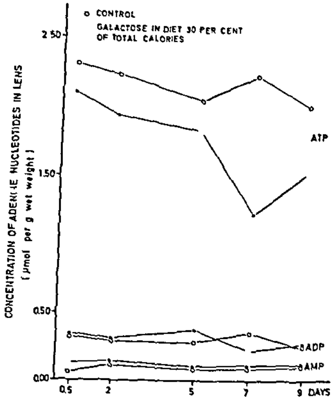


Fig 3

Adenine nucleotides in lenses during feeding control diet and galactose diet (30 % of the calories)

Discussion

The cataractogenic effect of galactose seems to be an accumulation of galactose galactitol or galactose 1 phosphate in the lens (Nordmann 1965) which causes an osmotic accumulation of water and a decrease in the content of reduced glutathion and ATP This leads to an impaired protein synthesis of the lens fibers (Sippel 1966 Philipson 1969) Morphologically these changes are followed by a hydropic swelling of lens fibres and loss of transparency (Kinoshita 1964)

The decrease in ATP concentration has been shown in other investigations (Lerman Devi & Hawes 1961) The constant concentration of ADP and AMP indicates that the decrease of ATP is a specific change due to galactose feeding and not just a relative decrease due to water accumulation The coincidence of the decrease in ATP concentration and the first ophthalmoscopical signs of cataract supports the hypothesis that a lowered concentration of ATP is an important pathogenic step in galactose cataract It is not evident however how galactose produces this reduction

The results demonstrate a positive correlation between the amount of galactose in the diet and the rate of cataract formation The dose response curve (Fig 2) indicates the existence of a threshold value of about 15 % of the calories as galactose for the development of nuclear cataract for cortical cataract it is below 15 % for the observation period used in this study More prolonged studies are required to decide if cortical cataract invariably develops into the nuclear form but the present observations are compatible with the concept that the difference between cortical and nuclear cataract is a question of time (Sippel 1966)

It seems likely that administration of galactose in excess of the elimination capacity leads to cataract formation Preliminary experiments indicate that the elimination capacity for galactose of the young adult rat is 500 mg per 24 hrs (Keiding & Tygstrup 1972) corresponding to about 1 % of the normal caloric intake In the normal diet of our laboratory rats galactose contributes 1 g per kg corresponding to about 0 1 % of the calories and in the young lactating rat 10 % (Spector 1965)

The observations also agree with the view that the determining factor is the galactose concentration in the blood since the rate of cataract formation was positively correlated with the measured concentrations despite the fact that the single determinations available can give only a rough estimate of the blood galactose content during the whole experimental period

On this basis it was expected that administration of ethanol which reduces the elimination capacity for galactose (Tygstrup & Lundquist 1962) would potentiate the cataractogenic effect of galactose The observations do *not* explain why this was not found to be the case but one reason may be that the total galactose intake was reduce by the ethanol contents of the diet since ethanol is known to reduce the appetite of rats (Richter 1926) In agreement with this the galactose concentrations were found to be independent of the ethanol contents in the diet Different ways of administering ethanol to ensure a constant sufficiently high concentration of ethanol in the blood independent of the galactose intake may be required *to answer* this question

Acknowledgments

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AN ANALYSIS OF THE FORCES DETERMINING THE SIZE OF THE PUPIL

BY

MARTIN DAVANGER

The constricting effect of sphincter and the dilating effect of dilatator vary inversely proportionally to the size of the pupil
The forces of dilatator and sphincter which determine the *size of the* pupil may be considered as analogous to the forces determining the caliber of a cylindrical elastic vessel namely the pressure in the vessel and the tension of its wall The equation $S = d \quad r$ is analogous to the law of Laplace $T \sim P \quad r$
The pupil is at rest when the force of dilatator is 2π times the force of sphincter This relationship is the condition of equilibrium
If from a state of equilibrium the force of one or both muscles *is* changed the pupil contracts or dilates until the condition of equilibrium as stated above is again established

Key words pupil – iris – sphincter pupillae – dilatator pupillae

The size of the pupil is determined by the relative state of contraction of the two muscles sphincter and dilatator pupillae These two muscles act antagonistically They are both in a state of permanent elastic tension which produces

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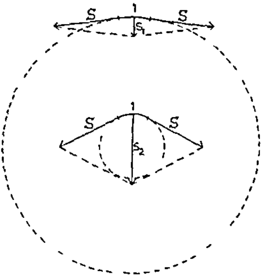


Fig 1

The centripetal constricting force s acting on a unit length of the pupillary circumference as a resultant of the force S of sphincter in a small and a large pupil

forces reciprocally counteracting each other However the mode of this reciproce counteraction and the relative size of the force produced by each of the two muscles when they are in equilibrium is not immediately evident

In equilibrium when the pupil is at rest the centripetally directed constricting force produced by sphincter and acting on a unit length of the pupillary circumference is equal to the centrifugally directed dilating force produced by dilatator and acting on the same length unit

The origin of the centripetal constricting force is the tension of sphincter This muscle pulls on both ends of the unit length with a force S which is directed tangentially Fig 1 demonstrates that the angle between the two forces acting on both ends of the unit length depends on the size of the pupil Hence their resultant the centripetally directed constricting force s is relatively larger when the pupil is small

This has been quantified by calculations carried out in the Appendix The calculations lead to the equation

$$s = S/r \tag{1}$$

where r is the radius of the pupil

From this follows that a certain increase in the force of sphincter leads to a larger increase in the constricting force when the pupil is small and vice versa That is from this point of view *the constricting efect of sphincter varies inversely proportionally to the size of the pupil*

When the pupil is at rest the dilating force d produced by dilatator and

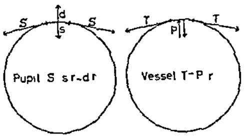


Fig 2
The analogy between the forces *determinin? the size of the pupil* and those deter mining the caliber of an elastic cylindrical vessel

acting on a length unit of the pupillary circumference is equal to s Then follows from equation (1) $\quad S = d \quad r$ (2)

As is demonstrated in Fig 2 the dilating force P produced by the pressure on a unit area of the wall of a cylindrical vessel mav be considered analogous to the dilating force d produced by dilatator and the transversal tension T *of the elastic vessel wall is analogous to the force of sphincter Thus it is seen* that equation (2) is analogous to the law of Laplace $T = P \quad r$

The size of the dilating force d in relation to the total force D of dilatator is elucidated by Fig 3 It is seen that when the pupil is small a wide sector of dilatator acts on our unit length and *vice versa* The relation between d and D may be calculated by noting that $d \quad 2\pi r = D$ that is

$$d = \frac{1}{2\pi} D/r \tag{3}$$

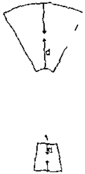


Fig 3
The size of the d lating force d acting on a unit length of the pupillary circumference in a small and a large pupil

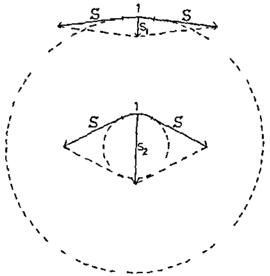


Fig 1
The centripetal constricting force s acting on a unit length of the pupillary circumference as a resultant of the force S of sphincter in a small and a large pupil

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The origin of the centripetal constricting force is the tension of sphincter This muscle pulls on both ends of the unit length with a force S which is directed tangentially *Fig* 1 demonstrates that the angle between the two forces acting on both ends of the unit length depends on the size of the pupil Hence their resultant the centripetally directed constricting force s is relatively larger when the pupil is small

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where r is the radius of the pupil

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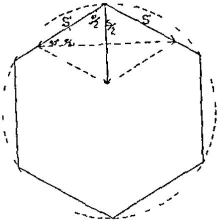


Fig 4
The centripetal constricting force s as a resultant of a force S directed along the sides of a regular polygon

Appendix

We consider the forces acting on the corners of a regular polygon Fig 4 The relation between a force S directed along the sides of the polygon and the resultant centripetal force s is given by

$$\frac{s/2}{S} = \sin(90° - \varphi/2) \qquad \text{(A1)}$$

where φ is the angle of the polygon s corners

In a polygon with n corners we have $\varphi = \frac{n-2}{n} \cdot 180°$ Then equation (A1) may be transformed to the general form

$$s = 2S \cdot \sin(180°/n) \qquad \text{(A2)}$$

The sum of the centripetal forces acting on all n corners is $s \cdot n = 2S\,n \cdot \sin(180°/n)$ When $n \to \infty$ the polygon approaches a circle and it can be shown that $n \cdot \sin(180°/n) \to \pi$ Therefore in the circular pupil the total constricting force acting on the pupillary circumference is $2\pi S$ where S is the force of sphincter The constricting force s acting on a small part of unit length of the pupillary circumference is

$$s = \frac{2\pi S}{2\pi r} = S/r \qquad \text{(A3)}$$

which is rather similar to equation (1) and shows in analogy with the similar law for sphincter, that *the dilating effect of dilatator varies inversely proportional to the size of the pupil*.

The relation between S and D is found by noting that s = d. Then by combining the equations (1) and (3) we find

$$D = 2\pi \cdot S \tag{4}$$

which means that in equilibrium the force produced by the collected dilatator is 6.28 times the force produced by sphincter.

This relation between the force of sphincter and of dilatator may be seen more directly by the fact that when the *radius of the pupil changes by an* amount Δr the length of dilatator changes by Δr while the length of sphincter changes by $2\pi \cdot \Delta r$. Then we have $D \cdot \Delta r = S \cdot 2\pi \cdot \Delta r$, hence equation (4).

From equation (4) it follows that $\frac{1}{2\pi}$ of the collected force D of dilatator is equal to S. That is, the force produced by a sector of dilatator of $\frac{360^\circ}{2\pi} = 57.3^\circ$ is equal to the force produced by sphincter.

It has been shown that *the pupil is at rest when the force produced by dilatator is 2π times the force produced by sphincter*. This condition of equilibrium is independent of the size of the pupil. If the condition of equilibrium is not fulfilled, the size of the pupil changes until the condition of equilibrium is re-established. For example, if from a state of rest the force of sphincter is reduced, the pupil must dilate. By this sphincter is stretched and its force increases, while at the same time dilatator is shortened and relaxed and hence its force is reduced. This process continues until the force of dilatator is again 2π *times the force of sphincter. Then the pupil is again at rest.*

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centre of the funnel shaped excavation of the disc there is a spot of dense white tissue which hides the course of the blood vessels in the depth of the papilla The vessels sometimes appear as multiple narrow branches coursing over the elevated annulus This congenital malformation is unilateral but other anomalies are often seen in the contralateral eye e g microphthalmos anterior chamber cleavage syndrome coloboma of the posterior pole and retinal detachment An optic disc of similar appearance was described by Gass (1970) in a patient showing persistent hyperplastic primary vitreous The retinal detachment occurring in the Morning Glory syndrome is not associated with retinal tears (Kindler 1970 Hamada & Ellsworth 1971) No solid subretinal tumour could be demonstrated by ultrasonography (Hamada & Ellsworth 1971) The histological picture of this anomaly has not been clarified but Pedler (1961) examined microscopically an eye with a possibly identical malformation

As the literature on the Morning Glory syndrome is very meagre three new cases studied clinically and by fluorescein angiography will be described in detail

Case reports

Case 1 A boy born in 1959 who had convergent strabismus of the right eye at birth When he was 2 years old an anomaly of the optic disc was observed at an examination which included fundus photography On re examination ten years later the picture was largely unchanged

Ocular findings at the age of 12 years Vision in the right eye = hand movements Convergent strabismus of the right eye by about 10 degrees Refraction −4 0 O cyl +1 0 ax 90° The horizontal corneal diameter was 11 5 mm The iris lens and vitreous were normal The large excavated optic disc contained a structure *less mass which centrally was* relatively dense and of a shiny white colour peripherally more opaque and faintly greyish pink No physiological cup was distinguished The disc was surrounded by a broad yellowish white zone forming a ring shaped peripapillary elevation The light zone showed scattered pigmentations No choroidal vessels were seen The retinal vascular pattern was abnormal (Fig 1) Some 20–30 vessels seen at the edge of the optic disc appeared not to be branches of a central retinal *artery or vein* They coursed over the light peripapillary tissue Only two or three veins were recognized with certainty the remaining vessels were of a nondescript type Many vessels ran a strikingly straight course as far as the semiperiphery where they ramified forming acute angles Above and below the optic disc moderate choroidal and retinal atrophy was observed The macular area was indistinguishable The retina was not detached Ophthalmoscopy of the deepest portion of the optic disc was performed with −5 0 D of the area nasally of the disc with −3 0 D and of the temporal area with −4 0 D

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THREE CASES OF THE MORNING GLORY SYNDROME

BY

ULF KRAUSE

Three cases of Morning Glory syndrome are described two of which were unilateral one bilateral Ophthalmoscopy revealed an enlarged optic disc surrounded by a typical elevated zone showing scattered pigmentations Vascular anomalies were observed in and around the optic disc as well as more peripherally Both narrow and larger abnormal blood vessels were seen *The narrow pathological vessels were better demonstrated by flu*orescein angiography than by ophthalmoscopy No pathognomonic vascular changes were discovered In one eye the retinal pigmentation was sparse peripherally with a distinct demarcation against the more normal pigmentation seen posteriorly All affected eyes were myopic which seems to *suggest that this error of refraction may be a characteristic of the Morning* Glory syndrome The anomaly does not necessarily cause marked diminution of vision Ectatic portions of the bulb were discovered ophthalmoscopically The Morning Glory syndrome appears to be a malformation involving not exclusively the blood vessels and optic disc

Key words Morning Glory syndrome – optic disc – vascular anomaly – fluorescein angiography – amblyopia – myopia – ectasia – retinal pigment

The Morning Glory syndrome which Kindler (1970) was the first to describe is characterized by a general enlargement of the optic disc which is surrounded by an elevated greyish annulus of chorioretinal pigment disturbance In the

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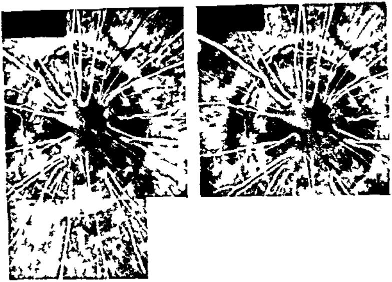


Fig 2

Case 1 Pair of stereophotographs The elevated peripapillary annulus is clearly seen At 1° o clock two veins unite to a larger vessel Note the acute angles of the ramifications and the peripapillary arcade like formations (arrows)

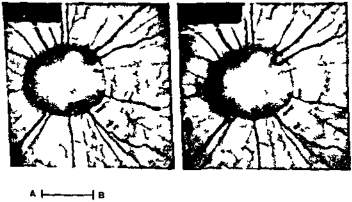


Fig 3

Case 2 Pair of stereophotographs showing the excavated optic disc with an elevated lighter area at the centre A peripapillary elevated annulus is seen A-B shows the papillary diameter of the normal eye at the same magnification

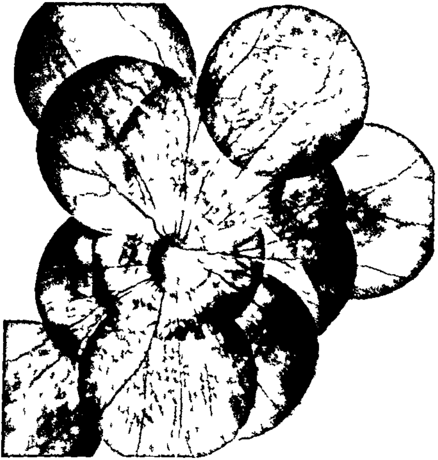


Fig 1

Case I Right ocular fundus with a central spot in the optic nervehead a peripapillary light area and numerous narrow blood vessels in part running a straight course Some vessels ramify forming highly acute angles

Vision in the left eye was 1.2 and refraction +1.25 O cyl + .75 ax 90° The horizontal corneal diameter was 11.5 mm The ocular findings were normal in other respects too

Fluorescein angiography of the right optic disc In the early arterial stage only slight fluorescence was seen in the disc and the light peripapillary zone Some ten very narrow and about as many somewhat larger arteries were recognized The venous pattern was similar but the vessels were not so numerous At 12 o'clock two veins seemed to unite to a larger vessel (Fig 2) while the remainder ran separate courses as far as they could be followed The narrow blood vessels often ran a straight course until they ramified and formed acute angles At the border of the disc very narrow blood vessels were seen in abundance and some arcade like formations were observed (Fig 2) The optic disc was surrounded by a gradually increasing diffuse fluorescence Darker well defined areas occurred in this fluorescent field No choroidal vessels could be distinguished

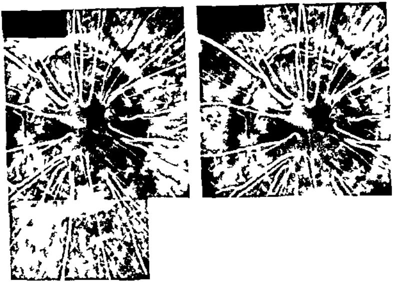


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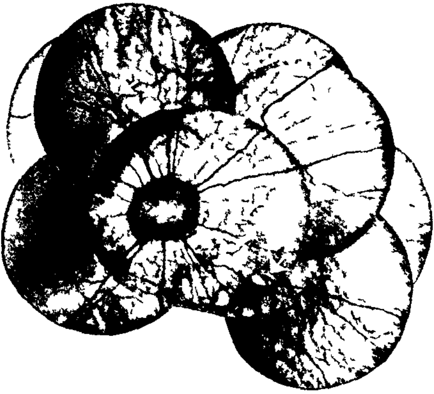
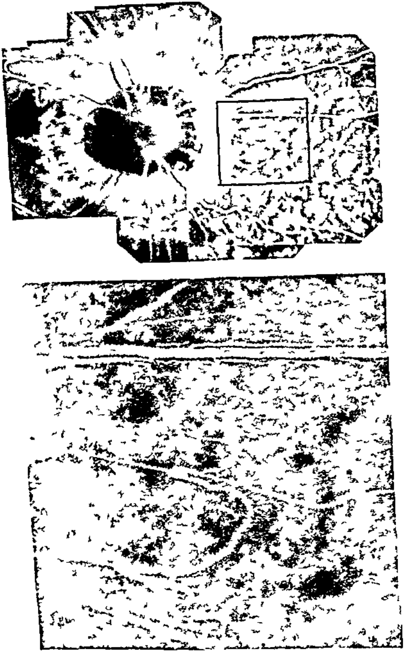


Fig 4

Case 2 Some narrow straight vessels (arteries as shown by fluorescein angiography) forming acute angles at the ramifications are seen The arrows show the location of S shaped vessels with a narrow straight vessel running at the distal most loop

Case 2 A boy born in 1957 Clinical findings at the age of 14 years Vision in the right eye 0 1 Refraction −4 0 O cyl +3 0 ax 90° There was no strabismus The horizontal corneal diameter was 12 mm The anterior chamber iris lens and vitreous were normal The excavated optic disc was enlarged (Fig 3) and contained a shiny yellowish white mass in the centre surrounded by pink structureless tissue The border of the disc was in part pigmented The disc was surrounded by a lighter zone forming a prominent annulus Scattered pigmentations occurred the choroidal vessels could not be followed as far as the edge of the disc The retinal vascular pattern was abnormal Numerous blood vessels ran over the peripapillary light elevation but their course in the depth of the papilla was hidden by the structureless tissue It was difficult in general to distinguish between arteries and veins but each quadrant contained at least one vein (Fig 4) that was somewhat larger than the other blood vessels Many extremely narrow vessels (ateries as judged by fluorescein angiography) ran a striking



Fi 5

Case Fluorescein angiogram showing weak fluorescence in the area of the optic disc The peripapillary area shows a strong diffuse fluorescence Partial magnification reveals narrow perivascula arterial ramifications

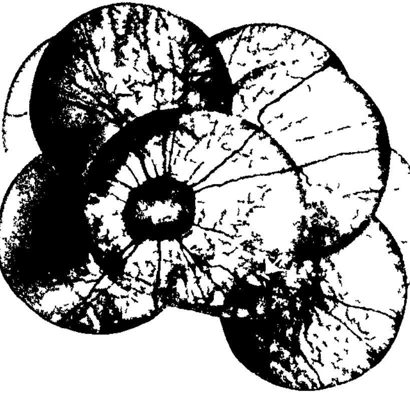


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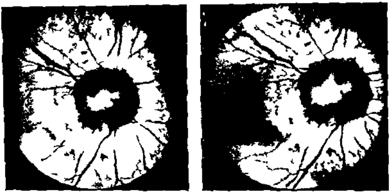


Fig 6
Case 3 right eye Pair of stereophotographs of the right optic disc. Large vessels are seen in the papillary area

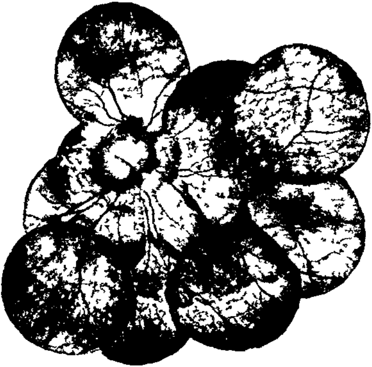


Fig
Case 3 left eye Nasally in the periphery the retinal pigmentation is deficient There is a distinct demarcation between this area and the normal retina

ly straight course towards the periphery Their scanty ramifications formed very acute angles At least three blood vessels with S shaped loops were seen In all these instances a narrow staight vessel ran just underneath the distal most loop Temporally of the disc evidence of a possible previous haemorrhage was detected in the deepest layer of the retina involving also the macular area (This haemorrhage was not seen on photographs taken one and a half years previously) No retinal detachment was observed The retina and choroid were sparsely pigmented and the choroidal vessels were visible over large portions of the fundus

The central portion of the optic disc was ophthalmoscoped with −8 0 D the peripapillary temporal portions with −1 0 D and the peripapillary nasal regions with −10 0 D Ophthalmoscopy of the area just under the macula was performed with −5 0 D

Vision in the left eye was 1 2 and refraction +2 25 O cyl +0 5 ax 90° The horizontal corneal diameter was 12 mm The cornea iris anterior chamber vitreous and optic nervehead were normal

Fluorescein angiography of the right eye The centre of the optic disc showed weak fluorescence throughout the examination darker edge almost none (Fig 5) The retinal vessels became visible at the border of the disc Some of them appeared to be branches of larger vessels hidden in the papillary tissue No central artery or vein was definitely distinguished The S shaped vessels were veins and a narrow artery was invariably recognized at the distalmost loop The peripapillary zone showed diffuse fluorescence throughout the examination No choroidal blood vessels were visible in this area

Case 3 A girl born in 1965 with a birth weight of 2660 g No oxygen therapy was given during the neonatal period Convergent strabismus and amblyopia of the left eye were observed at the age of 3 years

Ocular findings at the age of 6 years Vision in the right eye 0 4 corrected with −2 0 O cyl +1 0 ax 110° Keratometry revealed corneal astigmatism with the rule 1 5 D ax 115° The cornea was of normal size The cornea anterior chamber lens and vitreous were normal *On ophthalmoscopy the optic disc seemed to be definitely enlarged* and showed a deep excavation (−10 D) containing an indistinct faintly bluish pink mass which was totally pigmented at the border No lighter spot was seen in the centre and a physiological cup was clearly distinguished (Fig 6) At the edge of the dish there was a slighly elevated zone forming an annulus Scattered pigmentations were seen in the peripapillary area and at 7 o clock there seemed to be a small more deeply located haemorrhage Some choroidal vessels could be followed a short distance into the peripapillary area The retinal blood vessels were in part visible at the border of the physiological cup but in part they were embedded in the pink papillary tissue Some vessels ramified in the usual way in the disc others formed tortuous anastomoses Many vessels could be identified *as arteries or veins Outside the papillary area the vascular* pattern was normal Large portions of the retina and choroid were sparsely pigmented A macular reflex was lacking there was central fixation The retina was not detached Fluorescein angiography showed a weak diffuse fluorescence in the central portions of the optic disc In the more cranial portions tortuous vessels the size of capillaries were seen in abundance The pigmented egde of the disc was not fluorescent Around the disc a strong diffuse fluorescence was seen

Left eye Vision was 0 1 and refraction −6 5 O cyl +1 5 ax 75 Keratometry revealed astigmatism with the rule 1 5 D ax 72° The cornea which was of normal size the

tion as shown by Kindler (1970) Vascular anomalies are common In all
the present new cases the optic disc was definitely enlarged and excavate
Except in the left eye of Patient 3 it was surrounded by an elevated zone wi
scattered pigmentations A pigmented annulus of the very conspicuous ty
described by Kindler (1970) was not observed but the right eye of Patient
showed this structure in less extreme form The optic disc contained varyi
amounts of a structure less pink mass the centre of which was in two instanc
occupied by a white spot of tissue Since all eyes showed vascular anomal
in the papillary area in particular a classification of these cases as variants
the Morning Glory syndrome seems justified

The differential diagnosis between this syndrome and other anomalies su
as megalopapilla (Franceschetti & Bock 1950 Badtke 1959) and choroidal co
boma was exhaustively discussed by Kindler (1970) As the present stu
brought out no new aspects of this question there is nothing to add

The course of the retinal vessels immediately distal to the lamina cribrifor
could be followed to an extent determined by the reative transparency of
abnormal tissue of the nervehead In those cases where the *white spot* v
non transparent the vascular pattern of the edge of the disc was highly path
logical and the main branches of the blood vessels could not be visualized w
certainty even with fluorescein angiography In the less abnormal cases
retinal vessels could be recognized as ramifications of larger vessels wh
were somewhat more clearly seen by fluorescein angiography than by ophth
moscopy In these milder cases in any event the observations corrobor
Kindler s (1970) assumption that blood is supplied by central retinal vessels a
not by ciliary vessels

Anomalies of the small vessels in or near the area of the optic disc
occurred In Case 3 tortuous narrow vessels were seen in great number in
papillary tissue and an abundance of radial vessels coursed over the edge
the disc The fluorescence was intravascular which seems to rule out a p
sible neovascularization (Wessing 1968) Arcade shaped vascular formati
round the disc were present in Case 1 This patient showed an increa
number of retinal vessels which mostly were narrow and ran a straight co
towards the periphery Handmann (1929) described a series of somewhat sim
papillary anomalies In his cases the course of the blood vessels was o
straight It is obvious however that the condition observed by Handm
was not the Morning Glory syndrome since he definitely stated that the o
disc was of normal size In addition to the above mentioned straight ves
Case 2 displayd veins with S shaped loops A drawing of Kindler s Ca
shows two similar vascular loops A lighter peripapillary area was obse
in all pathological eyes It was yellowish white with scattered pigmentati

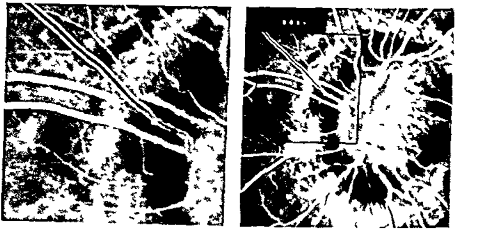


Fig 8

Case 3 left eye Fluorescein angiogram The edge of the optic disc is not fluorescent The retinal vessels seem to be ramifications of a ventral artery and vein Partial magnification shows narrow radial vessels at the edge of the papilla

anterior chamber lens and vitreous were normal Ophthalmoscopy revealed a markedly enlarged deeply excavated (-15 D) optic disc (Fig 7) with a clearly distinguishable physiological cup Centrally the disc was of normal colour but the edge was definitely greyish pink This area formed an incomplete annulus lying deeper than the surrounding retinal tissue Surrounding the disc except temporally above there was a lighter not elevated area containing some sharply demarcated pigmentations The macular region was distinguishable There was extrafoveal fixation The retinal blood vessels could be followed in the papilla and a common central artery and vein were faintly seen A classification into arteries and veins was sometimes difficult The vascular pattern outside the disc was normal the vessels coursed over the extrapapillary light mass of tissue The ocular fundus except the disc was examined by ophthalmoscopy using – D Above and nasally the peripheral portion of the retina was sparsely pigmented and showed a distinct demarcation against more normal pigmentation On fluorescein angiography the optic disc showed a diffuse fluorescence centrally This area was surrounded by a non fluorescent zone corresponding to the darker edge of the disc Surrounding the disc there was a moderately fluorescent area within which no choroidal blood vessels were distinguished Very narrow radial vessels coursed in great number over the cranial half of the dark edge of the disc (Fig 8) Their origin and further course could not be established

Discussion

The most typical features of the Morning Glory syndrome are an enlarged excavated optic disc and a surrounding elevated annulus of chorioretinal pigment disturbance The details of this general picture show considerable varia

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RELEASE OF FIBRINOLYTIC ENZYMES FROM HUMAN CORNEA

BY

M PANDOLFI B ASTEDT & K DYSTER AAS

The release of fibrinolytic agents from human cornea was studied by culturing foetal corneal explants in the presence of a standard fibrin clot and measuring the fibrin degradation products formed in the culture medium Cultures of cornea were found to invariably release a significant amount of fibrinolytic agents probably fibrinolytic activators since Tranexamic acid an inhibitor of plasminogen activation into plasmin completely blocked the dissolution of the clot in the culture system The function of these fibrinolytic activators is presumably to keep the cornea free from fibrin deposits which may occur after injury or inflammation

Key words cornea – tissue cultures – fibrinolysis – wound healing

The recent discovery of the collagenolytic properties of corneal epithelium (Slansky et al 1968) has revealed new aspects of corneal pathophysiology Evidence now available strongly suggests that injured corneal epithelium releases agents capable of cleaving collagen fibers with stromal damage as a result (Slansky & Dohlman 1970)

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not sclera coloured as in choroidal coloboma The demarcation against the normal tissue was indistinct Except in Case 3 left eye this area was elevated over the retinal plane and formed an annulus round the optic disc as shown by stereoscopic photography *This is in agreement with Kindler s findings*

In all eyes with Morning Glory syndrome so far described visual acuity has been markedly diminished An anomaly of the ocular fundus predisposes to amblyopia In unilateral cases an examination of vision therefore may not reveal the maximum capacity of the affected eye Case 3 was bilateral but the anatomical changes were slight vision being 0 4 in one eye The conclusion may be drawn that a diminution of vision moderate in degree is consistent with the Morning Glory syndrome

All of the eyes with Morning Glory syndrome in this report were myopic and astigmatic Hence it may be assumed that this error of refraction is typical of the syndrome Kindler gave no data on the refraction of his patients The shape of the ocular bulb was not spheric in all eyes as appears from the varying need of correction when adjacent areas were examined ophthalmoscopically

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sponge (Spongostan®) and cultured as organ culture in a separate Leighton tube containing 1 ml Parker 199 medium and a preformed standard fibrin clot produced by addition of 0 02 ml thrombin (Topostasin® 75 NIH U/ml saline) to 1 0 ml human fibrinogen (fibrinogen Kabi 1 % in distilled water Astedt et al (1971)) The explants were not in contact with the clot Twenty one cultures were prepared in this way The remaining 3 corneas were divided into pieces about 1 mm in diameter and placed on gelatin sponge and cultured in the same system Two additional cultures of sclera were prepared in this way A diagram of the culture system is given in Fig 1

During culture fibrinolytic activators were released from the explants into the medium They diffused to the clot causing a transformation of its plasminogen into plasmin with fibrinolysis as a result Every 24 hrs after the beginning of the culture a small volume (0 06 ml) of medium was aspirated and assayed for fibrin degradation products (FDP) with a quantitative immunochemical method (Nilehn 1967) The amount of FDP found was taken as a measure of the amount of fibrinolytic enzymes released by the explants A control consisting of gelatin sponge without explants was run for each culture experiment

To two culture systems with whole discs of cornea an inhibitor of fibrinolysis (Tranexamic acid AMCA 1 mg/ml Parker 199) was added

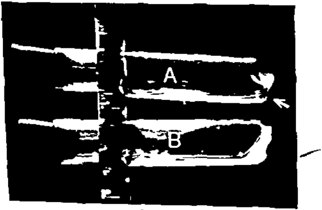


Fig 2

Two Leighton tubes at the fourth day of culture In tube A containing culture of cornea dissolution of the fibrin clot in contact with the culture medium is visible (arrow) No lysis of the fibrin clot in the control tube B

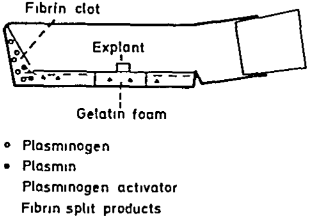


Fig 1
Diagram of the culture system For explanation see text

Pandolfi & Astrup (1967) demonstrated that in addition to containing collagenase corneal epithelium also contains fibrinolytic enzymes as does corneal endothelium They suggested that the fibrinolytic activity of corneal epithelial and endothelial cells plays a role in tissue repair by preventing excessive or permanent deposition of fibrin following exudative processes or hemorrhages

Both collagenolytic and fibrinolytic activity of cornea have hitherto been studied by means of film techniques i e by evaluating fibrinolytic activity from the lysis produced by corneal cells on a film of collagen or fibrin This investigation deals with the release of fibrinolytic agents from cornea with a new method permitting quantitative measurement of fibrinolytic activity

Materials and Methods

The material consisted of 24 corneas from 13 foetuses obtained by abdominal hysterotomy of healthy mothers in whom pregnancy had been terminated on sociomedical grounds The reported week of gestation ranged from 17 to 24 and the crown heel length from 14 to 27 cm Immediately after extraction of the foetus the eyes were enucleated under sterile conditions and placed in a sterile Petri dish containing Parker 199 (Statal Bacteriological Laboratory Stockholm) With the aid of a dissecting microscope the corneas were excised care being taken to cut well within the limbus With the epithelial layer uppermost each corneal disc was afterwards placed on a slice of gelatin

sponge (Spongostan®) and cultured as organ culture in a separate Leighton tube containing 1 ml Parker 199 medium and a preformed standard fibrin clot produced by addition of 0 02 ml thrombin (Topostasin® 75 NIH U/ml saline) to 1 0 ml human fibrinogen (fibrinogen Kabi 1 % in distilled water Astedt et al (1971)) The explants were not in contact with the clot Twenty one cultures were prepared in this way The remaining 3 corneas were divided into pieces about 1 mm in diameter and placed on gelatin sponge and cultured in the same system Two additional cultures of sclera were prepared in this way A diagram of the culture system is given in Fig 1

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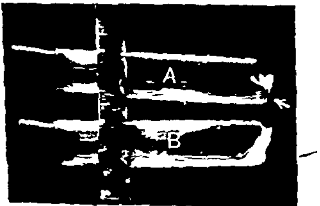


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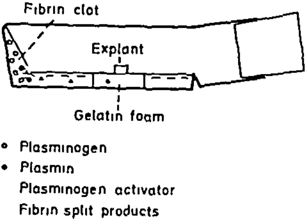


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During culture fibrinolytic activators were released from the explants into the medium. They diffused to the clot causing a transformation of its plasminogen into plasmin with fibrinolysis as a result. Every 24 hrs after the beginning of the culture a small volume (0.06 ml) of medium was aspirated and assayed for fibrin degradation products (FDP) with a quantitative immunochemical method (Nilehn 1967). The amount of FDP found was taken as a measure of the amount of fibrinolytic enzymes released by the explants. A control consisting of gelatin sponge without explants was run for each culture experiment.

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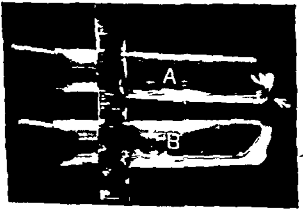


Fig. 2
Two Leighton tubes at the fourth day of *culture*. In tube A containing culture of cornea dissolution of the fibrin clot in contact with the *culture* medium is visible (arrow). No lysis of the fibrin clot in the control tube B.

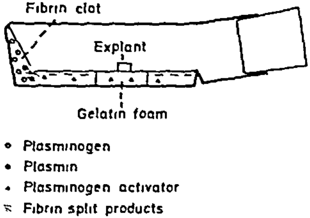


Fig 1

Diagram of the culture system. For explanation see text.

Pandolfi & Astrup (1967) demonstrated that in addition to containing collagenase, corneal epithelium also contains fibrinolytic enzymes as does corneal endothelium. They suggested that the fibrinolytic activity of corneal epithelial and endothelial cells plays a role in tissue repair by preventing excessive or permanent deposition of fibrin following exudative processes or hemorrhages.

Both collagenolytic and fibrinolytic activity of cornea have hitherto been studied by means of film techniques, i.e. by evaluating fibrinolytic activity from the lysis produced by corneal cells on a film of collagen or fibrin. This investigation deals with the release of fibrinolytic agents from cornea with a new method permitting quantitative measurement of fibrinolytic activity.

Materials and Methods

The material consisted of 24 corneas from 15 foetuses obtained by abdominal hysterotomy of healthy mothers in whom pregnancy had been terminated on sociomedical grounds. The reported week of gestation ranged from 17 to 24 and the crown heel length from 14 to 27 cm. Immediately after extraction of the foetus the eyes were enucleated under sterile conditions and placed in a sterile Petri dish containing Parker 199 (Statal Bacteriological Laboratory, Stockholm). With the aid of a dissecting microscope the corneas were excised, care being taken to cut well within the limbus. With the epithelial layer uppermost each corneal disc was afterwards placed on a slice of gelatin

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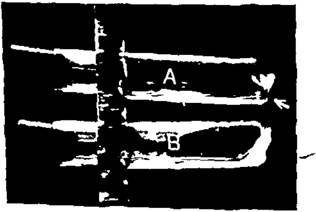


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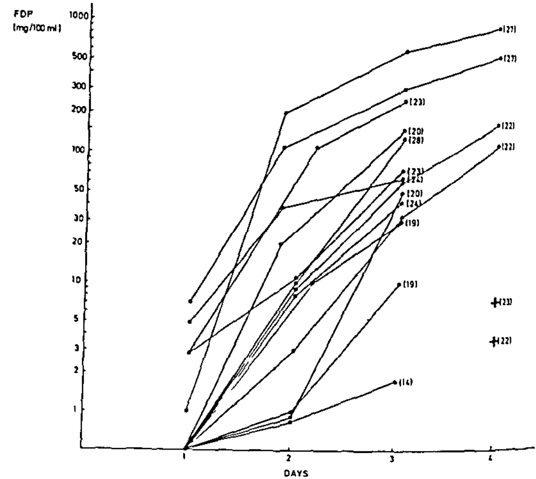


Fig 3

Fibrin degradation products (FDP) appearing in increasing amounts in the culture media of foetal corneas Ordinate (logarithmic) FDP in mg/100 ml Abscissa day of collection of media after the beginning of culture The two crosses denote FDP in culture media of sclera The crown heel length (in cm) of the donor foetuses are given in brackets

Results

Six cultures were discarded because of infection or spontaneous dissolution of the control clots Otherwise FDP regularly appeared in increasing amount in the medium of the cultures of whole discs as well as of fragments (Figs 2 and 3) No apparent correlation was found between the length of the donor foetus and the degree of fibrinolytic activity The two cultures of fragmented corneal explants showed comparable fibrinolytic activity (see Fig 3 the two corneas from foetus 24 cm long) Practically no FDP were demonstrated in the culture medium of the controls i e gelatin sponge alone A low degree

Table I

Inhibiting effect of AMCA on the fibrinolytic activators released by corneal cultures Cornea I and II belong to foetuses with crown heel lengths of 27 cm and 19 cm respectively Fibrin degradation products (FDP) (expressed in mg/100 ml) progressively increase in the culture media of cornea but appear in negligible amounts only at the fourth day of culture in the media containing AMCA and in the controls

	I	II	III	IV
Cornea I	0	0	240	480
Cornea II	3.5	75	160	336
Cornea I + AMCA	0	0	0	9 0
Cornea II + AMCA	0	0	0	0
Control	0	0	0	0 8
Control + AMCA	0	0	0	0

of fibrinolytic activity was exhibited by the two cultures of sclera at the fourth day of culture (Fig 3) Addition of AMCA to the medium prevented the dissolution of the clot (Table I) Conventional histological sections showed a good survival of the epithelium of the corneal discs but also a moderate

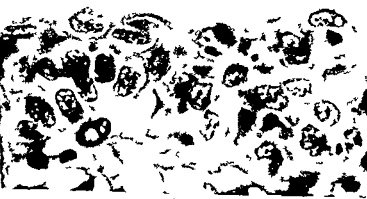


Fig 4
Good survival of the epithelial corneal cells after 4 days of culture Cytoplasmatic oedema and nuclear pyknocytosis of the underlying layer (× 375)

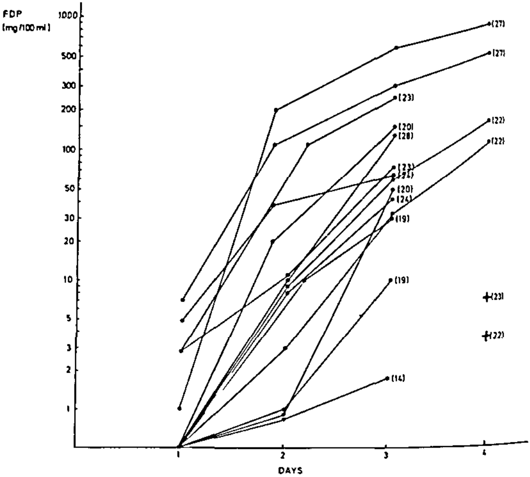


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vacuolisation of the stroma with pyknocytosis of the keratocytes (Fig 4) Fragmented explants showed no such stromatic changes but their epithelium was often detached

Discussion

The results show that human foetal cornea cultured *in vitro* releases soluble fibrinolytic enzymes in an amount capable of dissolving large quantities of fibrin Although the investigation does not teach anything about the types of the cells releasing the enzyme they are probably corneal epithelial cells and possibly also endothelial cells since histochemical studies have shown these two layers to contain plasminogen activator (Pandolfi & Astrup 1967) Cultures of separate corneal layers may help to identify the cells releasing the fibrinolytic agent

The epithelium covering whole discs of cornea survived well but that covering the fragments was often missing It is possible that during the process of division the epithelial cells have been damaged and become detached during culture Such epithelial damage had no demonstrable effect on the fibrinolytic activity of the culture which was comparable to that of whole discs of cornea

The complete inhibition of fibrinolysis obtained by addition of AMCA suggests that the agent liberated is an activator of plasminogen since AMCA affects fibrinolysis mainly by exerting a competitive inhibition of plasminogen activators and in the concentration used (1 mg/ml) it has no significant inhibitory effect on endopeptidases such as plasmin and trypsin (Andersson et al 1971) This finding is in good agreement with a previous observation on the failure of imprints of epithelial corneal cells to produce lysis on a fibrin film not containing plasminogen (Pandolfi & Astrup 1967) It also shows the possibilities offered by the method in the study of the behaviour of fibrinolytic activity of the cornea after addition of active compounds to the culture medium

Although the function of fibrinolytic enzymes of cornea in pathophysiology is not known it seems reasonable to assume that plasminogen activator liberated after corneal injury converts the plasminogen present in tears (Storm 1955) and in exudates into plasmin which clears the avascular cornea of undesired fibrin deposits Plasmin in wounded corneas may also contribute to produce chemotactic polypeptides since soyabean trypsin inhibitor a substance with antifibrinolytic activity has been shown to prevent polymorphonuclear invasion of injured corneal areas (Weimar 1957) Being quantitative and suitable for pharmacological studies the method described above may prove useful in elucidating the release of fibrinolytic activators from cornea

Ointment emulsions with oil in water (cooling ointments") irritate the eye Eyelid eczema and some cases of blepharitis are treated with steroid containing ointments There is a theoretical possibility that prolonged application of steroid ointment on the lid with consequent possible penetration into the conjunctival sac may provoke intra ocular hypertension and irreversible visual field loss in predisposed individuals

With a view to assessing these possible risks I have studied whether dyed ointment applied on the palpebral skin can penetrate into the conjunctival sac

Material and Method

A total of 96 eyes from 54 patients received 105 applications The dye used was in most cases the fat soluble red Sudan III or the corresponding bluish black Sudan black Fluorescein was used in seven cases In nine cases two dyes were employed at different sites of the same lid The dye concentration was 1 % throughout

The ointments applied were pure petroleum jelly in 8 cases oculentum simplex in 12 (80 % petroleum jelly plus 20 % liquid paraffin) equal parts of petroleum jelly and liquid paraffin in 37 soft lanolin ointment in 7 and peanut oil in 41

The patient was instructed to keep the eye carefully closed during the application of the ointment

The dyed ointment or oil was applied with one finger on the closed lid The ointment was in some cases rubbed – as in blepharitis – along the lid in its entire breadth In other cases the rubbing was confined to a certain local area the skin around the inner canthus or the outer canthus or on the middle part of the palpebral fissure The ointment was then removed with cotton and the eye was examined in the slit lamp a few minutes after the application and again 10 minutes later

Results

After application of ointment on the lid and subsequent removal with cotton considerable residues of ointment were left on the skin along the lid margin between lashes and on scales Foam formations at the inner and outer canthi were often stained by the ointment

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EYELID OINTMENT PENETRATING INTO CONJUNCTIVAL SAC

BY

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By rubbing dyed ointment into the palpebral skin along the lid margin of the closed eye transition of ointment to precorneal film and conjunctival sac was demonstrated in 54 % of 105 applications The ointment entered most often at the inner or the outer canthus
Where rubbing into the corners of the eye was avoided appreciable amounts of ointment were detectable in no more than 3 %
The penetration of the ointment seems to be independent of its melting point (petroleum jelly mixture of petroleum jelly and liquid paraffin peanut oil)

Key words eyelid ointment – ointment – side effects – penetration – Sudan – mucous thread – conjunctival sac

Ointment applied on the eyelid may in some instances penetrate into the conjunctival sac This may be unfortunate in case the ointment irritates the conjunctival sac or if the active substance provokes ocular side effects

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Discussion

The soft liquid peanut oil might be conceived to penetrate more easily into the eye than petroleum jelly which has a higher melting point

That no such difference exists may be because the ointments used become soft during the rubbing and the lid temperature ensures sufficient softness to allow ointment to penetrate inside the lid

The investigation showed that ointment applied on the palpebral skin penetrates most easily into the conjunctival sac through the inner or the outer canthus blinking causes ointment drops to be thrown into the sac or to be converted into foam which can pass into the conjunctival cavity Ointment from the middle part of the lid margin is less liable to enter the eye

Ointment from the palpebral skin is rarely seen to penetrate the eye in any considerable amounts Provided application of the ointment at the inner and the outer canthus is avoided the chance of penetration to any appreciable extent is no more than 3 %

On the other hand it must be emphasized that the present study has shown that eyelid ointment *can* penetrate into the eye

Hence the use of strong steroid ointments always involves a risk of steroid induced glaucoma

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Dyed ointment drops in contact with the eye were observed in half of the cases (54 %) Such ointment drops were noticed in the lacrimal river along the lid margin and in the precorneal film Within a few minutes all the ointment drops were caught by the mucous thread in the inferior conjunctival fornix where they were seen as coloured beads on an invisible string If present in large numbers the drops were found all the way from the outer to the inner canthus

Blinking caused the ointment drops to move with the mucous thread onto the skin at the inner canthus in the course of 30 to 60 minutes (Norn 1964)

In most cases the amount of ointment in the conjunctival sac was small However in 15 % of the whole material so much ointment was found that the amount present along the mucous thread was judged to be approximately equal to that covering a corresponding area of the palpebral skin The mucous thread area is of the order of 5 mm (Norn 1963)

The penetration of the dyed eyelid ointment into the conjunctival sac seemed to be independent of the melting point of the ointment base and of the fat soluble Sudan dye used The water soluble fluorescein perhaps penetrates more readily and spreads immediately in the aqueous phase

The penetration of the ointment depends on the site of application By usin for instance red Sudan medially and black Sudan laterally on the skin around the canthi it is possible to clarify whether the ointment enters from the medial or the lateral corner of the eye in the individual case

In 49 cases ointment was applied at the inner or the outer canthus and in 33 cases it was applied along the middle part of the lid margin avoiding the extreme parts

Ointment in the conjunctival sac was most frequently seen after application at a corner of the eye (65 %) whereas it was seen relatively seldom after application on the middle part even though the ointment stained the ciliary region (in 21 %) The difference is statistically significant ($p < 0.01$) No significant difference was noticed between the inner and the outer canthus

A fairly large amount of ointment (amount along the mucous thread approximately equal to that on the skin) was found in 20 % after application on the skin at a canthus *as against in 3 % after application on the middle* part of the lid

In 32 supplementary experiments ointment was applied gently on the palpebral skin without rubbing and left there throughout the experimental period (1–4 hours) Ointment was found in the conjunctival sacs of six eyes and first appeared 10 10 20 30 60 and 60 minutes respectively after the application

secretion probably is important for an optimal lubrication between conjunctiva and cornea Attempts to estimate the amounts of mucous secretions do not seem to have occurred in the literature

Mucous production calculated from the turn-over of goblet cells

The total daily mucous production in the conjunctiva can be calculated from the number of goblet cells their average volume and the time the cell needs to empty itself

Autoradiography using S[3] labeling of the mucous has revealed that the intestinal goblet cells in animals excrete approximately their volume in 24 hours (Jennings & Florey 1956) The conjunctival goblet cell appears to have a function similar to those of the intestine (Kessing 1968) for which reason a similar turnover time probably applies

The volume of the goblet cell varies with its localization in the conjunctiva However it is reasonable to equate the cells with spheres having an average diameter of 15 μm (Kessing 1968) The volume of a conjunctival goblet cell can therefore be estimated at 1400 μm^3 ($4/3\ \pi r^3$)

The density of goblet cells in the conjunctiva also varies with the location an average figure being 100 cells per 0 1 mm (Kessing 1968) The total area of the conjunctiva is about 15 cm (Ehlers 1965a) and the total number of goblet cells can therefore be calculated to be about $1\ 5 \times 10^6$

One and a half million goblet cells each with a volume of 1400 μm^3 is equivalent to a total intracellular mucous volume of 2 2 μl (= mm^3)

In 24 hours the amount secreted corresponds to the total intracellular volume viz the mucous production is about 2 μl per day in each eye

Mucous production calculated from the movement of the mucous thread in the inferior fornix

By means of blinking movements the conjunctival mucous becomes concentrated in the inferior fornix as the mucous thread (Norn 1969) With continued blinking it moves towards the inner canthus The production of mucous can be calculated from the dimensions and the rate of movement of the mucous thread

The mucous thread measured on a glass slide after alcian blue staining and embedding in glycerol has a width of 0 21 mm and a thickness of about 10 μm (Norn 1969) The movement of the mucous thread observed in the slit lamp after vital staining of its medial half (Norn 1969) was found to be 1 1 mm per minute (Norn 1969)

The mucous production can therefore be calculated to be $1\ 1 \times 0\ 21 \times 0\ 01$

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QUANTITATIVE AMOUNTS OF CONJUNCTIVAL MUCOUS SECRETION AND TEARS

BY

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Normal conjunctival mucous production amounts to about 2-3 μl/day in each eye estimated from the goblet cell turn over and from the movement of the mucous thread in the inferior conjunctival fornix
Normal tear secretion is 2-3 ml/day in each eye calculated from dye dilution tests and from corneal epithelial cell desquamation
The ratio between the amounts of mucous and serous secretion in the conjunctival fluid is on the order of 1 to 1000

Key words conjunctival fluid – goblet cells – mucous secretion – tears

The conjunctival fluid is composed of mucous and serous secretions The mucous is produced by the conjunctival goblet cells (Kessing 1968) whereas the serous secretion originates mainly from the lacrimal gland It is assumed that the goblet cell requires a certain amount of serous secretion for its normal function (Florey 1960) because a hydration of the mucous is important

The purpose of the present paper is to estimate the normal amounts of mucous and tear production The quantitative ratio between the two types of

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about 1 1000 This ratio between the amounts of mucous and tears present in the conjunctival sac will apply at any given moment only if complete mixing takes place

It is possible that the ratio between mucous and tears may vary in the different parts of the conjunctival sac In the precorneal film tears dominate while mucous dominates in the retropalpebral space (Ehlers 1965B Kessing 1967)

Deviations from the normal ratio seem to occur in keratoconjunctivitis sicca with reduced tear secretion but increased mucous secretion and in conjunctival pemphigus with reduced mucous production but probably normal tear secretion (Norn 1972) In keratitis increased amounts of mucous occur corresponding to the extent of the lesion in dry spots on the cornea the amount of tears is reduced In the event of further development (dellen) increased amounts of mucous may occur (Norn 1972)

The ratio between the amount of mucous and tear flow may thus alter under various pathologic conditions and cause the cornea or the conjunctiva to be both more poorly lubricated and less adequately protected

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mm³/min = 0 0023 mm³/min corresponding to 3 3 μl per day in each eye.

The first calculation is based on the amount of intracellular mucous The latter calculation is based on the amount of mucous which has been excreted from the goblet cells swelled in the conjunctival fluid and finally collected as the mucous thread in the inferior fornix Hydration and possibly later a dehydration may have taken place The calculations are too uncertain to allow any conclusions regarding the degree of swelling

From both calculations the mucous flow may be estimated to be 2–3 μl per day in each eye

Tear production

Several methods allow a determination of the tear flow The amount of tears may be calculated from the number of desquamated corneal cells and their concentration in the conjunctival fluid (Ehlers 1967) From the data of Norn (1966) a concentration of 572 non keratinized nucleated squamous cells per μl can be calculated Assuming that the cornea represents 25 % of the area in the conjunctival sac covered with squamous cells it may be estimated that about 2 million squamous cells are desquamated every day equaling 1 390 cells/min An average tear production of 2 4 μl/min may therefore be calculated

Nover & Jaeger (1952) studied the tear secretion after staining with 2 % fluorescein The dilution of the dye after two minutes was measured colorimetrically after collection in filter paper An average of 10 μl/min was found in normal eyes

Norn (1965) added 10 μl of a 1 % fluorescein Rose bengal solution to the conjunctival fluid After 5 minutes the dilution of dye in the lacrimal river corresponds to an average secretion of tears of about 10 μl/min

These varying normal values probably reflect mainly differences in the experimental conditions The basal tear secretion will be found with the more refined methods Any standardized method may however be used clinically e g that of Norn (Brandt & Fritsche 1967)

The basal tear production probably is about 1–2 μl/min or 2–3 ml per day in each eye

Discussion

Based on the above considerations it must be assumed that in a normal eye the production of mucous is about 2–3 μl per day the tear production 2–3 ml per day The ratio between mucous and tear secretion in the conjunctiva is thus

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CHEMICAL AND MECHANICAL DISSOLUTION OF HUMAN SENILE CATARACTS IN VITRO

BY

JAMES KLEIN and EDWARD COTLIER

The effects of mechanical and chemical dissolution on 100 human senile cataracts were tested *in vitro* Senile cataracts obtained immediately after surgical removal were grouped in three classes according to transparency color and hardness (resistance to perforation) Dissolution of the lenses by various chemicals during push pull aspirations was tested by weighing and by photography of cataracts before and after treatment Mechanical forces deaggregated senile cataracts depending on the specific cataract types Guanidine hydrochloride in 1 Molar concentration accelerated the rate of cataract breakdown *in vitro*

Key words cataract – chemical dissolution mechanical dissolution

Human senile cataracts causing decreased visual acuity are currently treated by the intracapsular surgical removal of the lens through a corneal limbal incision Although good visual results are obtained on most occasions the operative and postoperative complications can lead to poor visual results (Theodore 1964) An alternative method would be a surgical procedure that would remove the cataractous lens by dissolution of its contents and evacuation through a needle This ancient method was popularized by Scheie and is presently used in infantile and

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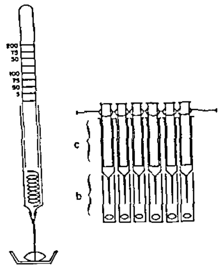


Fig 1

a – Dynamometer graded in 25 gms increments with attached 20 gauge needle piercing through cataractous lens b – Glass chambers containing cataractous lenses and chemical solutions tested c – Set of six syringes connected by a rigid wire used by the operator to inject and withdraw flu d simultaneously from all six chambers

1b) was attached to an apparatus consisting of a set of 6 disposable syringes and 20 gauge needles to test simultaneously 6 lenses in as many chambers (Fig 1c) The syringes were connected by a rigid wire and operated manually at a rate of ten aspirations per minute 2 cc in each aspiration over a ten minute period After 1 3 5 and 10 minutes of aspiration the lenses were removed from the chamber and photographed After 10 minutes the lens remnants were weighed The final cataract weight was expressed as a percentage of the initial cataract weight

Chemicals

The following chemicals were used guanidine hydrochloride+ guanidine chromate* guanidine thiocyanate* guanidine aluminum sulfate* urea+ sodium chloride° d glucose+ dithiothrietol+ and triton x 100+

+ Sigma Chemical Company
Anhydrous NaCl from J T Baker Chemicals 0 9 NaCl from Abbott Laboratories
Eastman Organic Chem als

juvenile cataracts (Scheie 1960) and in dislocated lenses (Maumenee & Ryan 1969) However a most formidable technical obstacle has prevented the needle aspiration of senile cataracts it is not possible to dissolve in isotonic saline solution the hard and gelatinous nucleus of a senile cataractous lens within a short period of time Lens dissolution however could be achieved by mechanical means if a chemical substance could simultaneously assist in the breakdown of the senile cataract s nucleus The experiments reported here deal with the mechanical dissolution of human senile cataracts *in vitro* as influenced by various chemical solutions Due to the heterogenous morphology and consistency of human senile cataracts a classification of progressive severity was designed and the rate of dissolution was tested in each cataract group Of the various chemicals tested attention was focused on the effects of guanidine hydro chloride This compound appears effective in deaggregating complex proteins *in vitro* (Tanford Kawahara & Lapanje 1967) as well as animal (Harding 1969) and human lens material (Pirie 1968)

Material and Methods

Each human senile cataract a total of one hundred was transported in saline solution (0 9 % NaCl) from the operating rooms of the Illinois Eye and Ear Infirmary to the laboratories immediately after intracapsular surgical delivery The age race and sex of the autopsy subjects and senile cataract patients was recorded Each lens was placed on graph paper (1 line per each mm) photo graphed on high speed Ektachrome (Kodak) film and weighed on a Mettler scale Hardness of each cataract (resistance to perforation) was measured after placing the lens on a petri dish and piercing through the lens center by means of a 20 gauge needle connected to a dynameter (Fig 1a) with a scale graded every 25 grams The cataracts were classified from the photographs according to color opacity and from the dynamometry measurements according to hard ness

Color 3 groups yellow yellow brown or brown

Opacity scale + to 3+

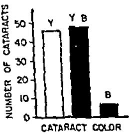
1+ one or more rows of graph paper grid visible

2+ less than one row of graph paper grid visible

3+ no visible graph paper grid

Hardness in 25 gram increments (from 25 grams to 200 grams)

After photography a cruciate incision was made through the lens capsule and stroma with a Wheeler knife and the lens transferred to a glass chamber con taining 5 cc of the chemical to be tested The glass chamber with each lens (Fig



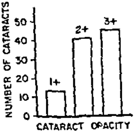


Fig. 3

Left Distribution of the 100 senile cataracts according to color Y yellow YB yellow brown and B brown.
Right Distribution of the 100 senile cataracts according to degree of opacity

were Negro and 67 % Caucasian The distribution of cataracts according to color is shown in Fig 3 (left)

Yellow and yellow brown cataracts were more predominant (46 % and 48 % respectively) than brown cataracts (6 %) The distribution of cataracts in various subclasses according to opacity is shown in Fig 3 (right) The majority of cataracts had advanced 2^+ and 3^+ opacities such as would be expected of cataracts obtained at surgery A bell shaped distribution of the cataracts according to hardness (Fig 4) had a peak at 100 grams Cataract hardness and cataract weight increased with age of the patients as seen in Fig 5 (left) and 5 (right) respectively

In Fig 6 (left) the correlates between hardness and color of the cataracts are shown Increased hardness was often associated with the darker cataracts A similar correlate was found between hardness and transparency of the cataracts (Fig 6 right) The more opaque cataracts were found to have the higher hardness values

Classification

After studying the correlations between the color opacity and hardness of the cataracts it became possible to place each cataract into one of three groups and therefore a three class grouping system was developed (Table I) Class I of yellow color 1^+–2^+ opacity and hardness of 75 grams or less class II of yellow

Rabbit Experiments

The toxicity of guanidine hydrochloride (1 Molar) to the rabbit anterior chamber was tested in two groups of rabbits

Group I Six rabbits received 100 microliters of 1 Molar guanidine hydrochloride (Gua HCl), osmolarity = 1600 mosmols, into the anterior chamber of the left eye after paracentesis and removal of an equal amount of aqueous humor with a 27 gauge needle The right eye was treated in similar fashion but injected with 5 % NaCl (1600 mosmols) The animals were observed daily for two weeks following which they were sacrificed and their eyes were processed for routine histology

Group II Five rabbits received 100 microliters of 1 Molar GuaHCl into the anterior chamber of the left eye after paracentesis and removal of an equal amount of aqueous humor A similar treatment was given to the right eye, but the solution was left in the anterior chamber 3 minutes following which it was irrigated out for 1 minute with 0 9 % NaCl The animals were observed at weekly intervals for two months

Results

HUMAN SENILE CATARACTS

The age distribution of 100 patients with the senile cataracts tested in this study in shown in Fig 2 The mean age was 65 9 years Forty four percent of the patients were males and 56 % females Thirty three percent of the patients

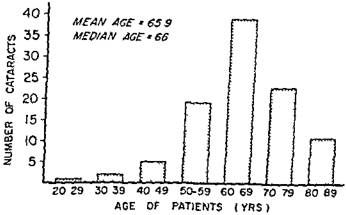


Fig 2

Age distribution of 100 patients with the senile cataract tested in this study

Table I

Human senile cataract classification system

	Opacity	Color	Hardness
Class I	1+–2+	Yellow	75 g or less
Class II	2+–3+	Yellow Brown	100 g to 1°5 g
Class III	3+	Yellow Brown or Brown	150 g or more

II the distribution of the 100 senile cataracts within the various classes is shown Most cataracts could be grouped easily into one of the subclasses and 90 % or more of the cataracts in each subclass fulfilled all the criteria in the classification

Cataract Dissolution

In preliminary experiments it was found that the cortical lens material of most cataracts could be brought into solution by the mechanical forces exerted during the aspiration maneuvers with either water or 0 9 % NaCl However the fragments of the lens nucleus (after the cruciate incision) were found resistant to dissolution in water or 0 9 % NaCl solution As the cortical areas compose 50 %

Table II

		Class I	Class II	Class III
Color	Yellow	100 %	32 5 % } 100 %	
	Yellow brown		67 5 % }	76 % } 100 %
	Brown			24 % }
Opacity	1+ opacity	34 4 % } 100 %	7 0 %	
	2+ opacity	65 6 % }	46 5 % } 93 %	100 %
	3+ opacity		46 [illegible] % }	
Hardness	75 g or less	93 7 %	4 7 %	
	100 g to 1°5 g	6 3 %	93 0 %	12 %
	150 g or more		[illegible] 3 %	88 %

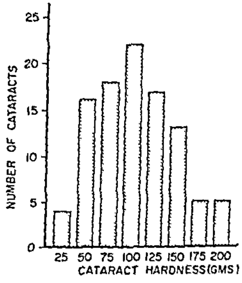


Fig 4
Distribution of the 100 senile cataracts according to hardness

and yellow brown color 2^+–3^+ opacities and hardness of 100–125 grams, and class III of yellow brown and brown color 3^+ opacities and hardness of 150 grams or higher The 100 senile cataracts studied were thus distributed as follows class I – 32 lenses class II – 43 lenses and class III – 25 lenses In Table

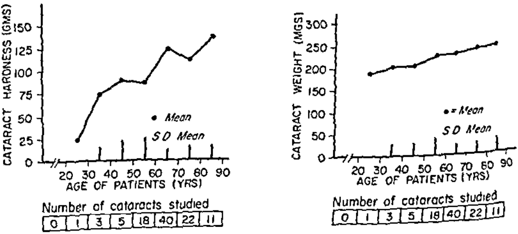


Fig 5
Left Relation between cataracts hardness (in gms) and age of the patients with these cataracts
Right Relation between cataracts weight (in gms) and age of the patients with these cataracts

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Table II

		Class I	Class II	Class III
Color	Yellow	100 %	32 5 % } 100 %	
	Yellow brown		67 5 %	6 % } 100 %
	Brown			94 %
Opacity	1+ opacity	34 4 % } 100 %	7 0 %	
	2+ opacity	65 6 %	46 5 % } 93 %	100 %
	3+ opacity		46 %	
Hardness	75 g or less	93 7 %	4 7 %	
	100 g to 125 g	6.3 %	93 0 %	12 %
	150 g or more		2 3 %	88 %

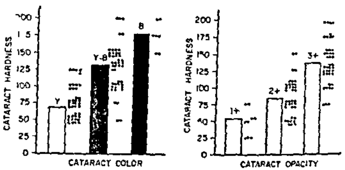


Fig. 6
Left Relation between hardness and color of the 100 senile cataracts Bars correspond to mean of each group Y = yellow Y B = yellow brown B = brown
Right Relation between cataract hardness and opacity of the 100 senile cataracts Bars correspond to the mean of each group

of the lens mass the mechanical forces could solubilize only this much of the cataracts

The chemical adjuvants tested in the cataract aspirations were selected on the basis of their effects on protein denaturation and solubilization Chemicals known to be harmful if placed into the anterior chamber of the eye such as strong acids or alkali were not tested 7 Molar urea was selected because of the known effect on deaggregating subunits of α crystalline (Bont, Jongkind, Wisse & Bloemendal 1962) Normal and hypertonic NaCl were used because of the combined ionic and hypertonicity effects on certain protein molecules (Joly 1966) Guanidine hydrochloride (Gua HCl) was selected on the basis of the findings by Harding (1969) and Pirie (1968) of solubilization of lens and cataract material respectively at the 6 Molar concentration Other chemicals tested included triton x 100 a detergent accelerating breakdown of cell membranes and lysosomes and dithiothrietol an –SH and S–S binding agent For detailed information on the effects of the chemicals selected in our study on proteins protein polysaccharide or protein pigment complexes the reader is referred to Joly s Physico Chemical Basis for Protein Denaturation (1966) the most comprehensive summary on this subject

To allow valid comparisons an equal number of cataracts from the three classes were tested by each chemical Balancing of each tested and control

group with an equal number of cataracts from each class was imperative because a gradient of faster solubilization class I ≫ class II ≫ class III was found regardless of the chemical used. The results of human senile cataract deaggregation from all classes using various chemical solutions are shown in Fig 7.

The effect of various chemical solutions on dissolution of senile cataracts expressed in % of total initial weight of the lens remaining after the experiment was (Fig 8)

1 Molar GuaHCl 12.7±10.5%, 5% NaCl 24.3±15.7%, 7 Molar urea 28.3±18.9%, 1600 mMolar glucose 29±19.3%, 6 Molar GuaHCL 30.8±19.7%, 0.9% NaCl 32±26.6%

The differences between 1 Molar GuaHCl and 0.9% NaCl were statistically significant ($P < 0.05$). The effect of chemical dissolution on cataracts of class I are shown in Figure 8 and the percentage of the original lens weight remaining after aspiration was in decreasing order 1 Molar GuaHCl 4±5.5%, Molar

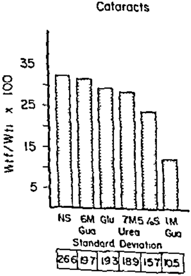
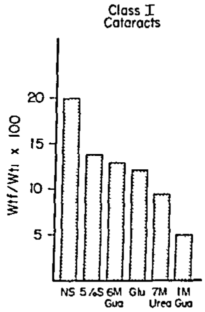


Fig 7

Effect of chemicals on dissolution of the senile cataracts. Wt f = final weight at the end of the experiment. Wt i = initial weight. NS = normal saline 0.9% NaCl. 6M Gua = 6 Molar guanidine hydrochloride. Glu = 1600 mMolar glucose. 7 M urea = 7 Molar urea. 5% S = 5% NaCl (1600 m osmolar). 1 M Gua = 1 Molar guanidine hydrochloride. Each bar corresponds to the mean of each group



Standard Deviation

62	84	47	88	127	55

Fig 8

Effect of chemicals on dissolution of senile cataracts of Class I Abbreviations similar to those of Fig 7 Each bar corresponds to the average of each group

urea 9 0 ± 12 7 % 1600 mMolar glucose 11 ± 8 8 % 6 Molar GuaHCl 12 6 ± 0 47 % 5 % NaCl 13 ± 8 4 % and 0 9 % NaCl 20 ± 6 2 % 1 Molar guanidine chromate 1 Molar guanidine thiocyanate and 1 Molar guanidine aluminum sulfate were tested in three cataract aspirations each but were found to be less effective than 1 Molar GuaHCl in dissolving the cataracts Further more addition of 50 mMolar dithiothrietol or triton x 100 to 1 Molar GuaHCl solutions (3 cataracts tested for each) did not accelerate dissolution as compared to 1 Molar GuaHCl alone

RABBIT EXPERIMENTS

Group I

Six rabbit eyes receiving 5 % NaCl developed the inflammatory reaction and formation of proteinaceous aqueous humor that follows paracentesis The con tralateral eyes of these animals received 1 Molar guanidine hydrochloride and developed corneal clouding beginning 48–72 hours after injection and continu ing for at least one week The corneas of the two animals become clear in two

weeks but two corneas were left with permanent opacities Two eyes receiving 1 Molar GuaHCl reacted similarly to those receiving 5 % NaCl Histology of eyes with corneal damage indicated the endothelium had disappeared in most areas and marked swelling of the corneal stroma had occurred The intraocular pressure of two eyes with corneal damage was found to be 10 and 8 mmHg (Schiotz)

Group II

Three of the left eyes of five rabbits receiving 100 microliters of 1 Molar GuaHCl developed transient corneal opacities lasting one to two weeks while one developed a permanent corneal opacity and one did not develop any corneal changes However the five contralateral eyes that received 100 micro liters of 1 Molar Gua HCl followed by normal saline irrigation for 1 minute developed neither transient nor permanent corneal opacities

Discussion

The goal of the present studies was to establish methods and guidelines for mechanical and chemical dissolution of human senile cataracts The reasons underlying such an approach are 1) to avoid the corneo scleral incision of 150–180 performed in the intracapsular lens extractions and thus decrease problems of corneal wound healing and sutures while shortening the convalescent post operative period 2) to avoid known complications of the intracapsular lens removal such as vitreous loss flat anterior chamber and associated secondary glaucoma macular edema or retinal detachments The overall incidence of these complications is 5 % to 8 % of all cataract extractions (Theodore 1964) and is most significant considering the large number of cataract operations per formed around the world However any cataract aspiration implies an extra capsular extraction and posterior opacities that may interfere with vision may be present in the posterior capsule These and other difficulties were en countered by Kelman (1970) who has removed human senile cataracts by aspiration after breakdown of the lens nucleus by ultrasound His procedure however does not appear practical enough and to this moment has not re placed accepted orthodox techniques for intracapsular lens removal

A selection of the chemicals to dissolve cataracts is without a proper theoretical basis due to the scanty knowledge of the chemical constituents and molecular organization of the dense and aggregated material in the abnormal

lens nucleus At least three main chemical pathologies occur in the nucleus of human senile cataracts 1) an increased concentration of insoluble protein as compared to the clear lenses 2) a firmer aggregation of the insoluble protein resisting solubilization (this may result from increased or chemically abnormal glycoproteins and increased hexosamine content has been found in senile cataracts (Auricchio & Daniele 1965)) and 3) the formation of a specific pigment recently characterized by Pirie (1968) The cataract pigment appears to be closely associated with or is a by product of glycoproteins and insoluble proteins Thus *chemicals intended to solubilize senile cataracts must* a) deaggregate the insoluble proteins, b) break down the abnormal protein bindings and deagglutinate protein glycoprotein complexes and c) break down the protein pigment complexes

In vitro it is apparent that the push pull mechanical forces exerted through the bathing fluids dissolved the cortical areas of the lens without difficulties. After the nucleus of the lens was broken down into smaller fragments by cutting it with a Wheeler knife the mechanical action of the aspirations reduced the size of these fragments Adjuvant chemical effects then hastened the dissolution of the lens Certain types of human senile cataracts were dissolved more easily than others Most susceptible to dissolution were cataracts with minimal opacities or yellow in color class I representing 32 % of the surveyed cataract population The correlates between hardness color and age would tend to indicate that cataracts in older patients dissolve with more difficulty

The use of our *classification for the human senile cataracts* proved of value for meaningful comparative studies The new system for human senile cataract classification proposed here is extremely practical and may be used to classify *cataracts before chemical determinations In addition slit lamp* examinations may allow classification of the cataracts in terms of the color and transparency and thus provide a pre operative evaluation of the cataract class in the event *that chemicals for safe in vivo needle aspiration of the lens become* available

In our experiments the mechanical forces contributed the major portion of the cataract dissolving effect" The amount of fluid 2 cc in each push pull aspiration was approximately *10* times the fluid that could be *injected* and withdrawn from the anterior chamber of the human eye The rate of push pull aspiration was 10 per minute or approximately two to three times the number of aspirations that would be performed if a human cataract was *removed* Furthermore each chamber contained *5* cc of fluid or approximately 20 times the fluid volume of the anterior chamber Experiments on cataract dissolution in a plastic human eye prototype where the volumes and method of needle aspiration simulate closely those *in vivo* are in progress Preliminary results would tend to substantiate the concept that the high mechanical forces used in

the above described experiments were responsible for such dramatic lens dis solutions

The above results indicate that 1 Molar solutions of GuaHCl hasten the mechanical dissolution of human cataracts especially in cataracts of class I It is of interest that the 6 Molar GuaHCl solution proved less effective than the 1 Molar GuaHCl solution Perhaps the extreme viscosity of the higher GuaHCl concentrations allowed less interaction between chemicals and the cataractous material In testing of chemicals for potential *in vivo* use the cataract dissolu *tion should* take place in less than 10 or 15 minutes with approximately 30 push pull aspirations Pirie (1968) tested the effects of 6M GuaHCl in the solubilization of decapsulated human senile cataracts ground in 2 ml of solvent and kept at 20 C for a period of 20 to 72 hours Within this experimental ar rangement she found that cataracts containing minimal pigment were com pletely solubilized whereas cataracts heavily pigmented were only *partially* solubilized The addition of 50 mMolar dithiothrietol to 6 Molar GuaHCl solubilized a majority of the lens material of heavily pigmented cataracts (Pirie 1968) We did not find dithiothrietol of help in the 10 minute solubiliza tion of senile cataracts either alone or combined with 1 Molar GuaHCl in seven tested cataracts However we did confirm the total solubilization of rat lens by 6 Molar GuaHCl reported by Harding (1969) and found similar total solubili zation of rabbit lenses in 6 Molar GuaHCl if left *decapsulated at room tem* perature for 24 hours

To dissolve rabbit lenses *in vivo* enzymatic agents such as hyaluronidase pronase (a proteolytic enzyme) or trypsin were tried in 1965 (by E Cotlier and B Becker unpublished) but the latter two were found to be extremely toxic to *the anterior segment of the rabbit* eye The fact that 1 Molar GuaHCl *produced* transient and in some rabbits permanent corneal opacities should contraindi cate its use in human eyes The search for more innocuous chemicals combina tions of chemicals or lower concentrations of GuaHCl may prove valuable It is encouraging that washing out the GuaHCl solution from the rabbit *anterior chamber with saline* prevented any corneal opacities

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COMPARISON OF BUPIVACAINE WITH AND WITHOUT ADRENALIN AND MEPIVACAINE WITH ADRENALIN IN INTRAOCULAR SURGERY

BY

V LAAKA P NIKKI and A TARKKANEN

A comparative double blind study has been made of 0.5 % bupivacaine (Marcaine®) with adrenalin 1 200 000 0 5 % bupivacaine plain and 2 % mepivacaine (Carbocaine®) with adrenalin 1 200 000 in a series of 35 patients undergoing cataract and glaucoma surgery
The onset time of analgesia did not differ in the groups but the onset of akinesia in orbicularis and especially in the extraocular muscles seemed longer in both bupivacaine groups
The duration of analgesia was about one and a half times as long and that of akinesia about twice as long in the two bupivacaine groups as in the mepivacaine/adrenalin group
In the bupivacaine plain group an increased tendency towards conjunctival bleeding was observable during the operation consequently bupivacaine with adrenalin is preferable
In ocular surgery 0 5 % bupivacaine with adrenalin offers a good choice of local analgesic agent when local anesthesia must last a long time Due to its slow onset the local blocks have to be administered at least 30 minutes before the surgery is begun

Key words bupivacaine – mepivacaine – ocular surgery

In intraocular operations temporary paralysis of the orbicularis oculi and the extraocular muscles together with blocking of the postganglionic fibres of the

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ciliary ganglion are essential for the prevention of serious damage Squeezing of the lids or movements of the eye could result in extrusion of the ocular content, and subsequent loss of the eye The safety of the operation would be further increased by the continuance of local anaesthesia during the early post operative phase as the patient then has time to recover from the operation and from the effect of premedication while the operated eye is still paralysed Consequently long acting postoperative analgesia and akinesia would be beneficial

A possibility for achieving long acting akinesia is the continuous administration of a local analgesic agent by means of a retrobulbar catheter (Scheie 1956) A simpler and safer method is the application of a local analgesic technique with a long acting agent such as bupivacaine (Marcaine®) It has been found that the effect of bupivacaine lasts about four times as long as that of mepivacaine (Löfström 1970) The duration of action of mepivacaine is somewhat prolonged by the addition of adrenalin whereas adrenalin does not alter the duration of bupivacaine (Löfström et al 1969) Only a few reports have been made on the use of these two local analgesics in ocular surgery (Kara et al 1961 Castrén 1963 Castrén & Tammisto 1966) Accordingly a report is made below on the results obtained in a double blind trial in which 0 5 % bupivacaine with adrenalin 0 5 % bupivacaine plain and 2 % mepivacaine with adrenalin were used on 35 patients subjected to operations for cataract and glaucoma

Material and Methods

A study was made of 35 patients undergoing cataract and glaucoma surgery Table I indicates their distribution in the three treatment groups Patients were premedicated intramuscularly with pethidine (Petidin® Star Oy) 1 mg/kg promethazine (Lergigan® Neofarma Oy) 0 5 mg/kg and atropine (Atropin® Orion Oy) 0 01 mg/kg 45 minutes before administration of local anaesthesia Local anaesthetic agents were injected double blind in coded ampoules A B and C containing 0 5 % bupivacaine (Marcaine® Bofors) with adrenalin 1 200 000 0 5 % bupivacaine plain and 2 % mepivacaine (Carbocaine® Bofors) with adrenalin 1 200 000 The code was unknown to any of the authors prior to completion of the study

LOCAL ANAESTHETIC TECHNIQUE

1) For analgesia of the orbicularis oculi muscle Atkinson s method (Atkinson 1953) was applied injections were made of 7 to 10 ml of bupivacaine with

Table I

Distribution of the material with regard to sex age height and weight

	Sex (M/F)	Age	Height (cm)	Weight (kg)	Dose (mg/kg)
Group A	3/9	66±3 9	163±3 1	74±4 0	0 82±0 03
Group B	9/2	64±2 5	172±3 2	74±4 1	0 81±0 03
Group C	7/5	65±3 0	163±2 7	64±4 0	3 75±0 20

Group A = 0 5 % bupivacaine with adrenalin Group B = 0 5 % bupivacaine plain and Group C = 2 % mepivacaine with adrenalin Means±SE are given

adrenalin bupivacaine without adrenalin and mepivacaine with adrenalin on the buccal side of the zygomatic arch near the periosteum

2) For paralysis of the extraocular muscles and for anaesthesia of the conjunctiva retrobulbar injections were administered of 1 5 to 2 0 ml of one of the three local anaesthetics

ASSESSMENT

Analgesia

Analgesia was assessed by means of a pin prick method Moreover the onset of the first subjective pain following the disappearance of analgesia was noted The quality of the analgesia was classified as follows

2 = analgesia or total loss of sensibility
1 = partial loss of sensibility
0 = full sensibility

Akinesia

The function of the orbicularis oculi muscle was tested by the same investigator who ordered the patient to close his eyelids

0 akinesia or total motor block
1 partial motor block
2 – full function of the orbicularis oculi muscle

Further to this the akinesia of the extraocular muscles was examined by asking the patient to look in the main directions of action of the rectus muscles

Table II
Onset of analgesia

Time (min)	0.5 % Bupivacaine with adrenalin	0.5 % Bupivacaine plain	2.0 % Bupivacaine with adrenalin
0–10	1	2	[illegible]
10–20	5	5	1
20–30			
≥ 31	2		
Totals (patients)	8	7	8

For scoring, the classification employed was the same as in testing the action of the orbicularis oculi muscle.

To test analgesia and akinesia, studies were made of the onset time, the degree of the block and the duration of the block. The onset time was tested every 10 minutes and the duration of the action every two hours. Consequently the duration of action is approximate; it was impossible to make more frequent checks of the parameters to be studied in view of the risk of postoperative complications.

In addition, records were made of the complications of local anaesthesia. All the assessments were made by the same investigator.

The statistical significance of the differences was studied by application of the Student's t test.

Results

ONSET TIME

Analgesia

It seems from Table II that the onset of analgesia is more rapid in the mepivacaine/adrenalin group, although no significant difference is apparent. Total analgesia was achieved in less than 10 minutes in 7 patients of the mepivacaine group, whereas in both bupivacaine groups this seemed to take more than 10 minutes. In the bupivacaine/adrenalin group 2 patients experienced onset of analgesia after a period exceeding 30 minutes.

Table III
Onset of akinesia of orbicularis muscle

Time (min)	0.5 % Bupivacaine with adrenalin	0.5 % Bupivacaine plain	2 % Mepivacaine with adrenalin
0–10		1	6
10–20	1	2	2
20–30	5	2	1
≧ 31	3	3	
Totals (patients)	9	8	9

Akinesia of the orbicularis muscle

(Table III) Akinesia seems to begin more rapidly in the mepivacaine/adrenal group Nine patients exhibited partial onset of akinesia in less than 10 minut and six patients total akinesia within a similar period in the mepivacai group however the time of onset of total akinesia in both bupivacaine grou was from 0–30 minutes and even longer in three patients of each group

Table IV
Onset of akinesia of the extraocular muscles

Time (min)	0.5 % Bupivacaine with adrenalin	0.5 % Bupivacaine plain	2 % Mepivacaine with adrenalin
0–10		1	6
10–20	9		4
20–30		3	
≧ 31		5	
Totals (patients)	9	9	10

Table V
Duration of analgesia (min)

	0.5 % Bupivacaine with adrenalin	0.5 % Bupivacaine plain	2 % Mepivacaine with adrenalin
From maximal onset until first sign of regression	292 ± 27 8 pts ×	307 ± 32 8 pts ××	217 ± 13 8 pts
From maximal onset until total regression	437 ± 38 8 pts ×××	451 ± 36 8 pts ×××	291 ± 13 8 pts

× $p < 0.05$
×× $p < 0.02$
××× $p < 0.01$

Akinesia of the extraocular muscles

(Table IV) The mepivacaine/adrenalin group exhibited a range in onset time from 0–20 minutes (in 6 patients less than 10 minutes) the bupivacaine/adrenalin group had a range of onset time from 10–30 minutes whereas bupivacaine without adrenalin prolonged the onset of akinesia in the extraocular muscles to an even greater extent exceeding 30 minutes in 5 patients

Table VI
Duration of akinesia of the orbicularis oculi muscle (min)

	0.5 % Bupivacaine with adrenalin	0.5 % Bupivacaine plain	2 % Mepivacaine with adrenalin
Loss of motility	215 ± 23 min 9 pts ××	230 ± 50 min 8 pts NS	106 ± 21 min 8 pts
Partial loss of motility	405 ± 31 min 9 pts ×××	432 ± 42 min 9 pts ×××	229 ± 10 min 8 pts

×× $p < 0.01$
××× $p < 0.001$

Table VII
Duration of retrobulbar anaesthesia

Time (hours)	0.5 % Bupivacaine with adrenalin	0.5 % Bupivacaine plain	2 % Mepivacaine with adrenalin
4			
4–6			4
6–8	5		
8–10	2	6	
Totals (patients)	7	6	4

DEGREE OF BLOCK

Analgesia

Satisfactory in all groups

Akinesia

The motor block remained partial in one patient in the mepivacaine/adrenalin group in 4 patients in the bupivacaine/adrenalin group and in 5 patients in the bupivacaine plain group

DURATION OF ACTION

Analgesia

In both bupivacaine groups analgesia lasted about one and a half *times as long* as that in the mepivacaine/adrenalin group In these bupivacaine groups the analgesia lasted about 300 minutes from maximal onset until the first sign of *regression* whereas the corresponding time in the mepivacaine group was 200 *minutes* The corresponding time from maximal onset until total regression in both bupivacaine groups lasted about 450 minutes and that in the mepivacaine/*adrenalin* group 290 minutes The differences were statistically significant (Table V)

Akinesia

It is observable from Table VI that the total loss of function of the orbicularis oculi muscle *in both bupivacaine* groups lasted about 200 minutes or twice as

long as that in the mepivacaine/adrenalin group The deviation in the bupivacaine group was so large that no statistical significance became apparent between this and that of the mepivacaine group In both bupivacaine groups the partial motor block lasted about 400 minutes or twice as long as that in the mepivacaine/adrenalin group This difference was statistically highly significant ($p < 0.001$) The duration of akinesia of the extraocular muscles did not exceed 4 hours in the mepivacaine/adrenalin group while in both bupivacaine groups it varied from 6 to 10 hours (Table VII)

COMPLICATIONS

No patient in any of the groups had retrobulbar haemorrhage An increased tendency towards conjunctival bleeding during the operation was observed in five patients in the bupivacaine plain group in one patient in bupivacaine/adrenalin group but in no patients in the mepivacaine/adrenalin group

Discussion

The important clinical characteristics in the evaluation of local anaesthetic agents are the onset time the degree of the block and its duration Previous studies have indicated that the onset times of bupivacaine and mepivacaine in different types of block do not differ (Albért & Lofstrom 1965 Ekblom & Widman 1966 Herbring 1966) The present authors did not find any distinct differences in onset time of analgesia between the two groups of bupivacaine and that of the mepivacaine/adrenalin group However the onset time of akinesia of the orbicularis and especially the extraocular muscles appeared to be longer in the bupivacaine groups than in the mepivacaine group A longer onset time particularly as concerns the blocking of motor impulses after bupivacaine has been observed by Bromage (1969) According to Lofstrom (1970) this tendency of bupivacaine may be an expression of lesser potency It needs also to be taken into account that in the present series the mean weight of the patients in the mepivacaine group was lower than in either bupivacaine group with the consequence that the dose of mepivacaine was correspondingly larger and thus the onset time possibly was shortened for that reason Nevertheless it appears that the retrobulbar block with bupivacaine should be administered more than 30 minutes before the operation is begun

In all groups the degree of sensory blocks was satisfactory except in respect of two patients in each group in whom the block was technically unsatisfactory The tendency to effect less intense a motor block in both bupivacaine groups indicates that bupivacaine is less potent than mepivacaine as was mentioned

The duration of blocks in the present series was comparable with observations made in previous studies However it should be emphasized that in this study the observation times were few because of the limitations imposed by the operation performed accordingly the results concerning both the duration of analgesia and that of akinesia are approximative We observed that in both bupivacaine groups the duration of analgesia and akinesia was about twice as long as that in the mepivacaine group a finding in conformity with earlier findings relating to different types of blocks (Albert & Lofstrom 1965 Herbring 1966 Hollmen 1966) In the present series the partial akinesia was somewhat longer in duration than the analgesia (from maximal onset until the first sign of regression) as in the study made by Hollmen in regard to axillary blocks (1966) No differences were discernible in the duration of akinesia and analgesia between bupivacaine/adrenalin and plain bupivacaine groups as had earlier been observed in epidural and different nerve blocks (Nishimura 1966 Nolte et al 1966 Nishioka 1967 Lofstrom et al 1969) The only difference apparent between bupivacaine/adrenalin and the plain bupivacaine groups was a more marked tendency towards conjunctival bleeding during the operation in the plain bupivacaine group This is attributable to the effect of bupivacaine in vasodilation and increase in blood flow (Åstrom 1965)

Bupivacaine thus appears to have a somewhat longer onset time but a duration about twice as long as that of mepivacaine/adrenalin in ocular anaesthesia Since adrenalin prolongs the duration of action of mepivacaine by about 100 % (Lofstrom 1970) presumably bupivacaine has a duration of action about four times as long as that of mepivacaine

If bupivacaine block is administered at least 30 minutes before the start of surgery the longer onset time arising from its use is not a disadvantage Long lasting analgesia and akinesia are of value after intraocular surgery as they prevent dangerous squeezing of the lids and eye movements Long acting local anaesthetics may also be used in connection with general anaesthesia which is followed more frequently by vomiting than is the case with local anaesthesia

The disadvantage of bupivacaine in comparison with mepivacaine is its action of vasodilation in ocular surgery Consequently it is recommended that adrenalin should be used with bupivacaine Some limitations are associated with the use of adrenalin as a vasoconstrictor for example when the patient is undergoing tricyclic antidepressant treatment It has been demonstrated that the effects of adrenalin are potentiated about three fold after the administra

tion of a tricyclic antidepressive agent (Svedmyr 1968) The effects exerted by adrenalin on metabolic and pulse rate increases are also potentiated after thyroid hormone treatment (Svedmyr 1966) The medical history of patients who are to undergo a block with bupivacaine/adrenalin is accordingly of importance

To conclude it may be stated that bupivacaine with and without adrenalin appeared to have a longer onset time but had a duration about twice as long as that of mepivacaine with adrenalin Bupivacaine may thus be of benefit in ocular surgery When bupivacaine is used it should preferably be in conjunction with adrenalin

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REPEATED APPLANATION TONOMETRY IN OPTIC ATROPHY

BY

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In eight cases with unilateral optic atrophy the decrease of IOP on repeated applanation measurements was found to be less in the eyes with optic atrophy than in the normal fellow eyes The consensual effect was reduced in the normal eye and normal in the damaged one

Key words optic atrophy – repeated applanation tonometry

When measured repeatedly the intraocular pressure (IOP) falls spontaneously on the eye measured as well as on the contralateral eye (Stocker 1958 Goldmann 1959 Moses 1961 Bechrakis 1966 and others) The mechanism causing this effect is not fully understood It cannot be a simple tonographic effect since the pressure increase caused by the applanation tonometer is very small Nor can the effect be attributed to changes in blood pressure since according to Bechrakis (1966) there is no correlation between these changes and the IOP decrease

Riise & Simonsen (1969) found that during the water provocation test the IOP did not increase to a normal extent in eyes with optic atrophy These authors suggested that the water exerted its influence via a centre in the hypothalamus and by efferent fibres in the optic nerve

The importance of the optic nerve for transmission of pressure effects caused by water and drugs has also been studied by Podos et al (1970)

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These observations initiated the present study of the pressure response to repeated applanation tonometry in eyes with optic atrophy

Material

The material consisted of two different groups one with eight cases with unilateral optic atrophy* (Table I) and another one with four cases with asymmetric cataract (Table II) In the first group the damaged eyes had pale optic discs and a vision of either zero (cases 1 2 4 5 7 and 8) or perception of light (cases 3 and 6) In all the damaged eyes there was an amaurotic or amblyopic pupillary response with one exception (case 1) in which there was an internal oculomotor paralysis In the contralateral eyes the optic discs and the visual acuity were normal The visual fields of these eyes were also normal except in case 3 in which there was a very small temporal hemianopia

In all cases of the second group the visual acuity was very low in one eye (Table II) Except for lens opacities these cases had normal eyes

Methods

After local anaesthesia with Novesin 0 4%® IOP was measured on one eye with a Goldmann applanation tonometer Then the other eye was measured once a minute for five minutes (six occasions) and finally the first eye was measured again After an interval of 15 to 30 minutes the procedure was repeated but the eyes were measured in the reverse order As a rule the measurements were made first on the eye with poor vision In cases 1 3 4 and 5 the procedure was repeated once or twice

Results

In all eyes with poor vision because of optic atrophy the decrease of IOP after repeated direct measurements was smaller than in the fellow eyes (Fig 1 Table I) If more than one series was made only the first series is given in

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* We are greatly indebted to Dr S E. Simonsen, who made it possible for us to measure three of the cases in group 1 (6 7 and 8). These cases are also included in the paper by Riise & Simonsen (1969)

Table I
Unilateral optic atrophies

Case No	Sex age (years)	Clinical legends	Decrease of IOP (mmHg)			
			Direct reaction		Consensual reaction	
			Poor eye	Fellow eye	Poor eye	Fellow eye
1	m 27	Meningioma from right optic nerve Extirpation with intraorbital optic nerve resection in 1968	0 1	3 4	2 0	1 0
2	f 3[illegible]	Suprasellar meningioma Extirpation with section of right optic nerve in 1970	0	3	3	1
3	f 51	Craniopharyngioma Right optic nerve severely damaged Partial extirpation in 1970	0 0 2	3 2 2	2 1 1	0 0 2
4	m 78	Ophthalmic zoster with atrophy of the left optic nerve in 1968	1 0	2 3	3 3	1 1
5	m 50	Orbital inflammation with atrophy of the left optic nerve in 1970	0 1	4 0	1 0	0 2
6	m [illegible]9	Head injury with atrophy of the left optic nerve in 1966	1	5	3	2
7	m 26	Head injury with atrophy of the right optic nerve in 1969	0	2	1 5	1 5
8	m [illegible]5	Head injury with atrophy of the right optic nerve in 196[illegible]	0	3	3	0

Table II
Asymmetric cataracts

Case No	Sex age (years)	Clinical legends	Decrease of IOP (mmHg)			
			Direct reaction		Consensual reaction	
			Poor eye	Fellow eye	Poor eye	Fellow eye
9	f 41	Asymmetric cataract Visual acuity 0 3 R E light localization L E	3	3	2	5
10	f 62	Cataract R E Visual acuity hand movements R E normal L E	4	4 5	2	3
11	f 67	Cataract I E Visual acuity normal R E light localization I E	5	3	4	3
12	f 74	Asymmetric cataract Visual acuity light localization P E 0 ? I F	3	3	3	2

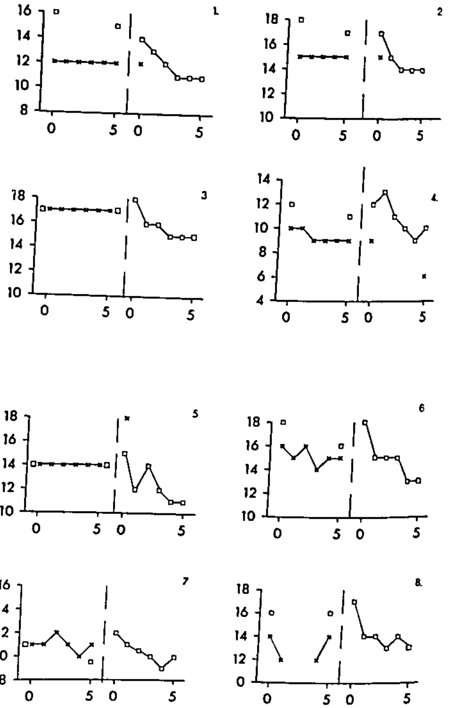


Fig 1

First series of measurements from eight cases with unilateral optic atrophy 1st measurement on one eye then 6 measurements 1 min apart on the other finally one measurement on the first eye (In case 2 only five measurements were taken on each eye) In case 7 it was impossible to obtain some consensual measurements due to blepharospasm and in case 8 a few measurements could not be made due to technical problems
× = lesion □ = normal

Fig 1 The mean curves of Fig 2 are also based on first series The average difference in decrease between the poor and the normal eyes was 3 1 mmHg (Fig 2) The average consensual decrease of IOP in the normal eyes was 0 9 mmHg (Fig 2) In the eyes with optic atrophy the consensual decrease was 2 4 mmHg which we consider normal The difference between the direct responses of the damaged and the normal eyes was tested with the simple sign test and found to be significant ($p > 0\,99$) The difference between the consensual responses is significant on the same level as well

In the cases with asymmetric cataract the direct and consensual decreases were normal in both eyes (Table II Fig 2)

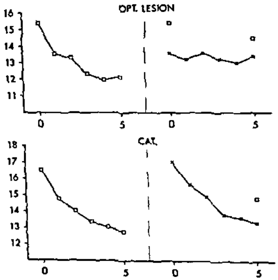


Fig 2

Above Mean series of *eight* cases with unilateral optic atrophy Below Mean series of *four* cases with asymmetric cataract × = poor eye □ = fellow eye

Discussion

In the cases of unilateral optic atrophy the pressure reduction upon repeated measurements was found to be less in the damaged eye than in the fellow eye This result suggests that nervous pathways in one way or another mediate the pressure decrease upon repeated tonometry Since no similar side difference

could be demonstrated in the cases with asymmetric cataract the reduced response could not reasonably be due to poor vision

In normal cases the consensual pressure reaction is almost as large as the direct response In the eyes with optic atrophy the consensual response was about as high as in totally normal cases (mean 2 4 mmHg) but in the fellow eye the consensual response was low (mean 0 9 mmHg)

In most of the cases (Fig 1 Nos 1 2 4 6 and 8) the IOP was somewhat lower in the damaged eye than in the normal eye It might be suspected that eyes which already have a lower pressure might react less than those with a higher IOP However the observation that the consensual effect on the damaged eye was of normal magnitude and the fact that normal cases with a low IOP (not included in this material) give a normal pressure response makes it unlikely that the IOP difference should be responsible for the difference in pressure reduction

It may be worth noting however that the pressure decrease obviously behaves similarly to the pupillary light reflex which suggests that the atrophy might involve a damage to centripetal fibres mediating the pressure decrease However our knowledge of which nervous paths are damaged is inexact and incomplete and the present small material cannot support any definite opinion on the mechanism involved

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THE EFFECT OF RETROBULBAR TISSUES ON THE ULTRASONIC FIELD

BY

ARVO OKSALA

Pig eyes and retrobulbar tissues were used in an experimental investigation of the effects on the sound field caused by the sclera with the optic nerve the sclera with some retrobulbar tissues attached to it and the retrobulbar tissues alone The optic nerve had a slight or considerable attenuating effect The attenuation produced by retrobulbar tissues which included the optic nerve fat and muscular tissues etc was considerably stronger than that caused by the optic nerve alone After the sound had travelled through the retrobulbar tissues the sound field was not only strongly attenuated but often also very irregular

Key words ultrasonic attenuation – ultrasonic field – optic nerve – retrobulbar tissues

In a B scan examination of the eye retrobulbar tissues reflect echoes from a depth of 10–15 mm The U or V shaped retrobulbar ultrasonogram consists of echoes reflected by muscular and fat tissues The optic nerve is represented in the ultrasonogram as an acoustically empty space (Baum 1965 Baum & Greenwood 1958 1960 Purnell 1966 1969) Diagnosis of orbital diseases is based primarily on the changes in shape that are observed in retrobulbar

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could be demonstrated in the cases with asymmetric cataract the reduced response could not reasonably be due to poor vision

In normal cases the consensual pressure reaction is almost as large as the direct response In the eyes with optic atrophy the consensual response was about as high as in totally normal cases (mean 2 4 mmHg) but in the fellow eye the consensual response was low (mean 0 9 mmHg)

In most of the cases (Fig 1 Nos 1 2 4 6 and 8) the IOP was somewhat lower *in the damaged eye than in the normal eye It might be suspected* that eyes which already have a lower pressure might react less than those with a higher IOP However the observation that the consensual effect on the damaged eye was of normal magnitude and the fact that normal cases with a low IOP (not included in this material) give a normal pressure response makes it unlikely that the IOP difference should be responsible for the difference in pressure reduction

It may be worth noting however that the pressure decrease obviously behaves similarly to the pupillary light reflex which suggests that the atrophy might involve a damage to centripetal fibres mediating the pressure decrease However our knowledge of which nervous paths are damaged is inexact and incomplete and the present small material cannot support any definite opinion on the mechanism involved

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a piece of tissue consisting only of the optic nerve and the retrobulbar tissues surrounding it This piece was 15 mm long All particles were prepared a couple of hours after slaughtering

The examination situations were as follows (1) The particle containing the posterior part of the sclera and the optic nerve was placed in the water bowl on a copper wire stand between the transducer and the steel ball so that the sound beam would hit the optic nerve after travelling through the centre of the calotte (2) The particle consisting of the posterior part of the sclera the optic nerve and the surrounding retrobulbar tissues was placed on the stand (3) The particle consisting of the optic nerve and the surrounding retrobulbar tissues was placed on the stand The shortest distance between the transducer and the ball was 40 mm and the ball moved at a distance of approx 3 mm from the cut end of the optic nerve Attempts were made to maintain the position of the optic nerve in relation to the transducer throughout the examinations

The control examinations of the sound field were made in plain water In the control measurements and when examining the effect of the posterior part of the sclera and the optic nerve on the sound field the amplification of the equipment that was used was db reserve = 40 The optic nerve with the surrounding retrobulbar tissues attenuated ultrasound so strongly that in order to register the echoes a considerably higher amplification had to be used i e db reserve = 10 when the effect of these tissues on the sound field was being investigated We used 20 different tissue particles in investigating the effects of the sclera with the optic nerve and the sclera with retrobulbar tissues The effect of the optic nerve with other retrobulbar tissues was investigated with 10 different tissue pieces

Results

All cross section measurements of the sound field gave very coherent and easily repeatable results which can be presented in the form of a few echo amplitude curves

The effect on the sound field produced by the posterior part of the sclera with the optic nerve and by the posterior part of the sclera with retrobulbar tissues

Fig 1 represents the highest measured attenuation in the sound field caused by the tissues mentioned above At the bottom of the picture one can see the results obtained in control measurements made in water The control tests produce a very regular sound field When the sound has travelled through

ultrasonograms Oksala & Häkkinen (1969) made a comparison between the attenuation of ultrasound caused on the one hand by orbital fat and muscular tissues and on the other hand by water The frequencies used were 6 and 8 MHz They found out that muscular tissue attenuates ultrasound somewhat more than water while the attenuation by fat tissue is considerably higher than that caused by the other two substances

In a study of the effect of the optic nerve on the sound field in a pig eye Oksala (1970) noticed that depending on the angle of incidence of the sound the optic nerve may produce an absolute or relative acoustic shadow or sometimes even amplify the sound pressure The amplification in the sound pressure is probably due to the focusing effect of the tissue under particular circumstances In a B scan examination Oksala & Jääslahti (1971) found out that depending on the angle of incidence of the sound the optic nerve may be seen to produce a relative or absolute acoustic shadow

In this study I have investigated besides the effect of the optic nerve also the effect of the surrounding tissues mainly fat and muscle on the ultrasonic field

Material and Methods

The apparatus used for the investigation was Kretztechnik s ultrasonic equipment model 7000 with an unfocused 6 MHz/8 mm transducer The ultrasonic equipment was supplied with a Tektronix oscilloscope 515 A for measuring the echo amplitudes

The measurements of the sound field were made in a bowl of water into which the transducer was immersed The transducer was fixed to a stand At a desired distance beneath the transducer an SKI steel ball with a diameter of 2 mm was moved The steel ball acted as a sound reflector The position of the steel ball in relation to the transducer could be determined in three directions to an accuracy of 0 1 mm The cross sections of the sound field were examined with a distance of 2 mm between them One of the cross sections fell together with the centre of the transducer Echo amplitude curves were then drawn on the basis of the amplitudes of the echoes reflected by the ball The amplitudes that were obtained were directly proportional to the sound pressures at the corresponding points in the field

For the examination we used pig eyes and retrobulbar tissues First we prepared a calotte of the posterior part of the sclera in which only a 15 mm long piece of the optic nerve was left Second a scleral calotte was prepared but this time in addition to the optic nerve some other retrobulbar tissues mainly muscular and fat tissues were left attached to it Third we prepared

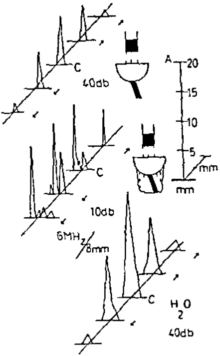


Fig 2

Represents the smallest measured attenuation in the sound field caused by the posterior part of the sclera plus the optic nerve as well as by the posterior part of the sclera plus some retrobulbar tissues

tissues was again so strong that the db reserve value had to be raised to 10 before clear echo amplitude curves could be measured In this situation the amplitudes obtained were however distinctly higher than the ones presented in Fig 1 The curves also contained several maxima and minima

The effect of the retrobulbar tissues on the sound field

Figs 3 and 4 represent the highest and smallest attenuation in the sound field caused by the optic nerve and the surrounding tissues The curves at the bottom show the control results obtained in water In these cases the sound fields are quite regular The attenuation caused by the retrobulbar tissues was always so strong that in order to register clear echoes we had to raise the amplification of the equipment to db reserve = 10 In this way it was possible to register a sound field with a diameter of 4 mm like the one presented in

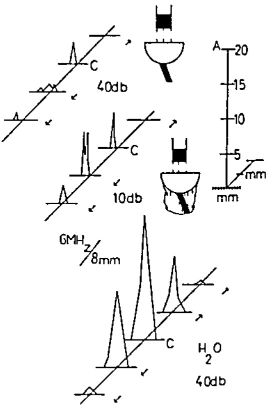


Fig 1

Represents the highest measured attenuation in the sound field caused by the posterior part of the sclera plus the optic nerve as well as by the posterior part of the sclera plus some retrobulbar tissues

the scleral calotte and the optic nerve with the same amplification (db reserve = 40) the result is a strong attenuation which is shown in the topmost three echo amplitude curves The curves in the centre were obtained when the sound passed through the sclera the optic nerve and the surrounding retro bulbar tissues The attenuation of sound was so strong that the amplification of the equipment had to be raised to a db reserve value = 10 before the echo amplitudes could be registered clearly

Fig 2 represents the smallest measured attenuation caused by the tissues mentioned above At the bottom of the picture we have the regular echo amplitude curves from control measurements The topmost echoes show that when the amplification used was the same as in the control examination the scleral calotte and the optic nerve attenuated ultrasound fairly little and the sound field was as regular in shape as it was in the control examination The combined effect of the posterior part of the sclera and the retrobulbar

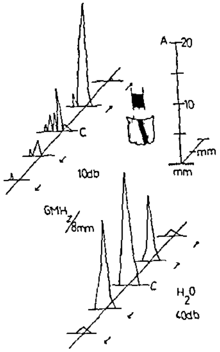


Fig 4
Represents the smallest measured attenuation in the sound field caused by the retro bulbar tissues

beam hit a scleral calotte nearly perpendicularly It was observed that the optic nerve attenuated ultrasound either distinctly or slightly The investigation was not however directed towards establishing situations where one could observe a total reflection of ultrasound or a possibly focusing effect of the optic nerve on the sound beam

Other retrobulbar tissues which were attached to the sclera attenuated ultra sound considerably more strongly (approx 30 db or more) than the optic nerve alone On the basis of earlier investigations (Oksala & Hakkinen 1969) it seems probable that fat tissue is the most important factor in the strong attenuation caused by the retrobulbar tissues The amount of attenuation that occurs when the sound travels through the retrobulbar tissues is not only due to the amount of tissues in the area of the sound beam but also to the angle of incidence when the sound beam hits the acoustical border surfaces inside the tissues

The investigation showed that retrobulbar tissues may both attenuate ultra

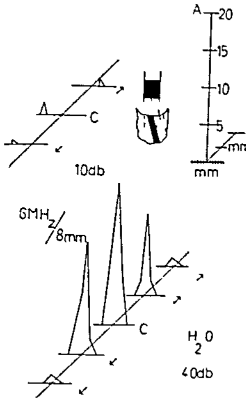


Fig 3

Represents the highest measured attenuation in the sound field caused by the retro bulbar tissues

Fig 3 The echoes reflected in this field were very low Fig 4 shows that under highly similar circumstances a retrobulbar tissue could in some cases attenuate ultrasound distinctly less than what is shown in Fig 3 After the sound had travelled through the retrobulbar tissues it was possible to register an 8 mm long and wide sound field at the edge of which a fairly high sound pressure was found The sound field was irregular in shape and contained several maxima and minima

Discussion

In an earlier paper (Oksala & Hakkinen 1968) the authors discovered that if the sound beam travels through the cornea or the sclera at a 90° angle of incidence these tissues cause only slight and clinically usually insignificant attenuation in ultrasound In the investigation mentioned above the sound

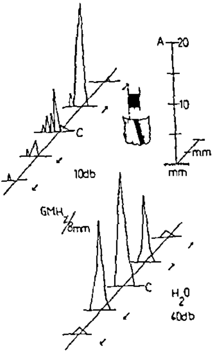


Fig. 4
Represents the smallest measured attenuation in the sound field caused by the retro bulbar tissues

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The investigation showed that retrobulbar tissues may both attenuate ultra

sound strongly and also make the sound field very irregular This is seen in Fig 4 where the maximal sound pressure was obtained from one edge of the sound field after the sound beam had travelled through retrobulbar tissues

On the basis of this experimental investigation in which only one unfocused transducer was used one should take into consideration for purposes of clinical ultrasonic diagnosis of the orbit that the retrobulbar tissues may attenuate ultrasound considerably and that the sound field that is available for diagnosis may be extremely irregular

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ACTA OPHTHALMOLOGICA VOL. 50 1972

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STUDIES ON RELATIVES OF PATIENTS WITH GLAUCOMA SIMPLEX AND PATIENTS WITH PSEUDOEXFOLIATION OF THE LENS CAPSULE

BY

PEKKA POHJANPELTA & LEENA HURSKAINEN

The occurrence of glaucoma and pseudoexfoliation of the lens capsule was investigated in 185 relatives, aged over 40, of patients with glaucoma simplex, glaucoma capsulare and normotensive pseudoexfoliation. The aggregate frequency of glaucoma and suspected glaucoma in the first group was 43, in the middle group 33 and the last group 9 %. Pseudoexfoliation of the lens capsule was seen in 3 % of the glaucoma simplex relatives and 8 % of the pseudoexfoliation relatives. The genetic aspects of the findings are discussed.

Key words: glaucoma capsulare – glaucoma simplex – pseudoexfoliation of the lens capsule – inheritance of glaucoma

Glaucoma simplex is known to occur hereditarily and its frequency is high among relatives of glaucoma patients (Demary 1960, Becker et al. 1960, Paterson & Miller 1962, François et al. 1966, Leighton 1968). There is also evidence of the heredity of pseudoexfoliation of the lens capsule (Tarkkanen 1962, Tarkkanen et al. 1965, Bertelsen 1966, Klouman 1967, Aasved 1969,

Received December 20, 1971.

Knape & Raitta 1970) Pseudoexfoliation and glaucoma simplex have been found in the same families (Tarkkanen Klauman)

The purpose of the present study was to investigate the incidence of glaucoma and pseudoexfoliation of the lens capsule in relatives of patients with glaucoma simplex and/or pseudoexfoliation of the lens capsule

Material and Methods

The study was based on 71 randomly selected patients with glaucoma and or pseudoexfoliation Their distribution by diagnosis was

– 22 patients had definite glaucoma simplex (open angle increased ocular tension cupped disc and a typical field defect)

– 31 patients had glaucoma capsulare (open angle glaucoma + pseudoexfoliation of the lens capsule) Of these 21 had cupped disc and field loss

– 8 patients had glaucoma capsulare in one eye and glaucoma simplex in the other In the analysis of the results their relatives are included in the glaucoma simplex group except for discussion of the frequency of pseudoexfoliation of the lens capsule when the findings are included in the glaucoma capsulare group

– 10 patients had pseudoexfoliation of the lens capsule and normal ocular tension

These patients siblings and children over 40 years of age were invited to present themselves for examination If a subject was already known to have glaucoma the matter was verified and the attending physician or hospital in question was approached for detailed information

The examination comprised visual acuity tension measurement by both applanation and Schiotz tonometer gonioscopy and after dilation of the pupil a slit lamp examination and ophthalmoscopy Irisangiography was not used in diagnosis (Vannas 1969) If the ocular tension was > 17 mmHg and/or the papilla was excavated tonography and visual field examination were added If the ocular tension was > 22 mmHg and/or if Po/C > 100 the subject was admitted to hospital for a diurnal curve and water drinking test

Subjects whose ocular tension was persistently (a minimum of three occasions) ≥ 26 mmHg or who met two of the following criteria were classified as affected with glaucoma ocular tension continuously ≥ 24 mmHg outflow < 0 13 tension increase after the water drinking test not less than 10 mmHg cupped disc field loss typical of glaucoma

Table I

Distribution of the series according to sex and the diagnosis of the index patients

	No of glaucoma simplex relatives	No of glaucoma capsulare relatives	No of normotensive pseudoexfoliation relatives
Women	48	43	14
Men	39	32	9
Total	87	75	23

Subjects whose ocular tension was ≥ 22 mmHg and/or Po/C was > 100 were classified as glaucoma suspects

The study covered 185 members of 71 families Table I shows their distribution according to sex and the diagnosis of the index patient Women were in the majority in all the groups

The mean age of the subjects was 57 1 years The age distribution is shown in Table II The youngest age class 40–49 years was the largest most of them were the patients children Most of the siblings belonged to the 60–69 year group which formed the second age distribution peak

Table II

Age distribution of the series

Age ranges	40–49 No	50–59 No	60–69 No	over 70 No	Mean age
Glaucoma simplex relatives	32	19	22	14	56 4
Glaucoma capsulare relatives	7	10	20	18	58 1
Normotensive pseudoexfoliation relatives	8	6	5	4	56.5
Total	6	5	47	36	57 1

Table III

Occurrence of diagnosed glaucoma suspected glaucoma and pseudoexfoliation in the series examined

	No examined	Glaucoma		Suspected glaucoma		Pseudoexfoliation	
		No	Frequency	No	Frequency	No *	Frequency **
Glaucoma simplex relatives (Group I)	87	15	17 %	22	25 %	2 (2)	3 %
Glaucoma capsulare relatives (Group II)	75	8	11 %	[illegible]	23 %	[illegible] (4)	[illegible]
Normotensive pseudoexfoliation relatives (Group III)	23	1	4 %	1	4 %	2 (1)	9 %

* Number of subjects with glaucoma or suspected glaucoma is shown in brackets

** For calculation of the frequency the relatives of glaucoma simplex patients with unilateral pseudoexfoliation were tranferred to Group II

Results

The results are presented in Table III The total frequency of glaucoma and suspected glaucoma among glaucoma simplex relatives (Group I) was 43 % among those of the glaucoma capsulare patients (Group II) 33 % and among relatives of the patients with normotensive pseudoexfoliation of the lens capsule (Group III) 9 % The difference between Groups II and III was statistically almost significant ($p < 0.05$ Student s t test) Apart from one possible angle closure glaucoma (the patient s hospital record was available but contained no mention of the angle) all the glaucomas and suspected glaucomas were of the open angle type

There were 24 cases of glaucoma Of them 15 belonged to Group I 8 to Group II and one to Group III The disease had been diagnosed earlier in 16 cases and only 8 were new The proportion of the patients aware of their disease therefore was high

Eight of the glaucoma patients had a field defect and a cupped disc. Six of these belonged to Group I one to Group II and one to Group III

In Group I one of the glaucomas (7 %) and one of the glaucoma suspects had pseudoexfoliation of the lens capsule In Group II the corresponding figure was two in both categories (25 % of the glaucomas) In Group III the only glaucoma had pseudoexfoliation of the lens capsule

The Group I glaucomas were distributed among 9 families Hence the disease occurred in the relatives of about 30 % of the patients with glaucoma simplex In Group II the number of families was 7 and the percentage about 20

Pseudoexfoliation of the lens capsule occurred in 3 % of the Group I subjects and in 8 % of the subjects in Groups II and III The difference is not statistically significant The subjects in whom pseudoexfoliation was found were over 60 years old except for a woman of 42 The frequencies in this age group are 7 % for Group I and 14 % for Groups II and III

Discussion

The frequency of glaucoma among glaucoma simplex relatives has been reported to range from 4 to 9 7 % and that of suspected glaucoma from 30 to 40 % (Demary 1960 Becker et al 1960 Miller Paterson 1962 *Leighton 1968*) simplex relatives 11 % among those of glaucoma capsulare patients and 4 % In the present study 25 % of the glaucoma simplex relatives were glaucoma suspects The figure is close to the percentages reported earlier

The frequency of glaucoma in the present study – 17 % among glaucoma among those of pseudoexfoliation patients with normal ocular tension – are only mutually comparable for they include as far as is known all those in whom glaucoma had been diagnosed already and almost 30 % of the family members invited to attend for examination failed to appear The true frequencies therefore are lower but still very high among the relatives of both glaucoma simplex and glaucoma capsulare patients Even assuming that there was no glaucoma among the subjects who did not attend the results would be 13 8 and 3 % The same factor has a contrary i e somewhat reducing effect on the frequency of glaucoma suspects The frequency of glaucoma in the glaucoma simplex relatives is higher than that reported by earlier authors This is due to the inclusion of the cases of glaucoma diagnosed earlier according to the medical histories

The frequency of glaucoma among the relatives of glaucoma simplex patients was higher than among those of glaucoma capsulare patients Statistically however the difference is not significant It becomes more pronounced if only

definite glaucomas are included i e the subjects who also had a cupped disc and field loss There were six in the former category only one in the latter The eyes with hypertension alone may of course contain eyes with no tru glaucoma

The majority of the index patients in the glaucoma capsulare group had bilateral hypertension and pseudoexfoliation Only in five was the fellow eye normal in this respect and therefore in most cases glaucoma simplex cannot be excluded In any case the results show that the relatives of not only patients with glaucoma simplex but also of those with glaucoma capsulare make up a risk group with a high frequency of increased ocular tension

It has been shown by topical cortisone instillation that glaucoma simplex and capsulare are not genetically identical (Pohjola & Horsmanheimo 1971) The present results are compatible with this finding but suggest that there may be some genetical connection as has been reported earlier (Tarkkanen 1962 Tarkkanen et al 1965 Kloumann 1967)

The relatives of normotensive pseudoexfoliation patients included only one with glaucoma and one with suspected glaucoma The small material makes appraisal difficult

Pseudoexfoliation without hypertension seldom responds with an increase in tension to topical cortisone instillation (Tarkkanen & Horsmannheimo 1966 Gillies 1970) The present results also suggest that this group of patients is genetically relatively glaucoma free

The frequency of pseudoexfoliation of the lens capsule in the relatives of glaucoma simplex patients was 3 % and among those over 60 it was 7 % This is close to unselected materials in which the reported incidence for subjects over 60 was 4 0–6 3 % (Aasved 1969) The corresponding frequencies among the relatives of patients with pseudoexfoliation were 8 and 14 % These figures confirm the earlier observations that the occurrence of pseudoexfoliation of the lens capsule depends on hereditary factors This accounts for a part of the high frequency of glaucoma among the relatives of the patients with glaucoma capsulare for as is well known elevated intraocular pressure is often associated with pseudoexfoliation

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TRANSACTION OF THE DANISH OPHTHALMOLOGICAL SOCIETY 1968–1969

BY

METTE WARBURG Secretary

(The publication of these transactions is regrettably delayed and a large part of the discussion is lacking because the collected reports were destroyed by fire at the end of 1969)

418th Meeting Oct 5 1968, in Copenhagen (Eye Clinic Rigshospitalet Blegdamsvej)

N Bulow and N Ehlers *Corneal Epithelial Cells in Tissue Cultures* Acta Ophthal *46* (1968) 749

H H Seedorff and J Edmund *Retinal Detachment IV*

M S Norn *The Mucous Thread in the Inferior Conjunctival Fornix*

A survey and demonstration of preparations The basic investigations have been published as follows

Acta Ophthal *46* (1968) pp 1125–1134 Cells and vacuoles in the mucous thread of the inferior conjunctival fornix

Acta Ophthal *46* (1968) pp 1113–1124 Metachromasia of conjunctival mucus – Toluidine blue staining of the mucous thread in the inferior conjunctival fornix

Acta Ophthal *47* (1969) 723–734 Birefringence of mucous fibrils in the mucous thread of the inferior conjunctival fornix Polarization microscopy

B Moestrup *Thin Corneae in a Patient with the Ehlers Danlos Syndrome* Acta Ophthal *47* (1969) 704

L Bartholdson O A Jesen B Johansson and K Mortensen *Teratoma of the Orbit* Publ as follows Bartholdson L Johansson B & Mortensen K Congenital teratoma of the orbit Scand J Plast & Reconstruct Surg *1* (1967) 90

O A Jensen *Teratoma of the orbit* Acta Ophthal *47* (1969) 317

419th Meeting Oct 25 1968 in Copenhagen (Eye Clinic Rigshospitalet Blegdamsvej)

P T Skov Louisianna USA (guest) *Removal of a Partially Dislocated Lens with a Calhound Hegler Pin*
Film and discussion

B Moestrup *Analysis of Greenlandic Patients Admitted During the Past 10 Years to the Eye Department Rigshospitalet Blegdamsvej University of Copenhagen*

P M Møller *Low tension Glaucoma*

The symptom complex of low tension glaucoma was briefly described with the characteristic glaucoma like changes of the disc and visual field but normal intra bulbar tension

Previous authors investigations into cupping of the disc without glaucoma were reviewed

Similar to H U Møller s case of a chordoma on Blumenbach s clivus with symptoms suggestive of glaucoma a patient with cupped disc nasal visual field defects and arcuate scotomas but a normal tension was demonstrated Operation had revealed a large chromophobic pituitary adenoma in the very site where bitemporal defects would be expected

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420th Meeting Nov 16 1968 in Copenhagen (Eye Clinic Rigshospitalet Blegdamsvej)

N Bulow *Pigment Epithelium of the Retina* Optic Effect

N Bulow *Colour Vision A Resonance Theory* Acta Ophthal *46* (1968) 1054

Discussion V *Dreyer and O A Jensen* N *Bulow*

V *Dreyer and O A Jensen* The extensive conclusions which in most respects depart from current opinion are based upon a single observation concerning the light scat tering properties of pigment granules in a tissue culture of human pigment epithelium Although in his discussion the author initially states that doubt may be thrown upon all presumptions he later assures that The theory is based on well established anato mical and physical factors and that his theory gives an exact and comprehensive explanation of most of the essential processes in retinal physiology

First some anatomical considerations As regards the size of the melanin granules in the retinal pigment epithelium we find it in no way exceptional that the size is within the range of the wavelengths of the visible light. Melanin granules of similar size are found in the iris stroma of the cat monkey and of man and the same *holds* true of the *granules* in the iris pigment epithelium of man. The size here may vary from 0 4 to 1 45 μ

It is true that the melanin granules of human skin are smaller being about 0 05

to 0 1 μ In some cutaneous areas however the so called compound melanosomes may be found to be up to 0 5 μ The size in these areas is therefore the same as the size of several granules of the retinal pigment epithelium

The size of the melanin granules in the cells of the substantia nigra are of the same order as that of the granules of the retinal pigment epithelium Pigment granules in cells of neural tube derivation are commonly larger than granules in cells of neural crest derivation Incidentally melanin granules in melanocytes of the human choroid may be found to be 0 8 μ The fact is therefore that in several areas outside the retinal pigment epithelium melanin granules are of a size that makes scattering of the light possible The question then is whether this scattering can be effective as a protection against undesired wavelengths of light In the skin protection – especially against ultraviolet rays – is desired Most granules here have a size exactly corresponding to the ultraviolet wavelengths

Bulow postulates a resonating cavity consisting of a wave guide with a light scattering particle at each end one of the particles being a melanin granule lying in intimate contact with the tip of the photoreceptor

The localization of melanin granules in cells is not however a static condition They are constantly being formed secreted and destroyed Further the organelles of the cytoplasm are in movement It is therefore far fetched to imagine a constant localization of a granule at the tip of the cone As concerns the intimate contact at least a layer of polysaccharide as well as a patch of the cytoplasm bounded by the cell membrane lie between the receptor and the granule The localization near the receptor of the granules in the cells of the retinal pigment epithelium supports just as well a light protecting hypothesis as it does a resonator hypothesis

It might be of interest to consider the function of melanin granules in other species for instance in the tapeta bearing species These use mainly various crystals in their tapeta to increase the sensitivity of the photoreceptors but they use melanin granules when screening must take place – the so called occlusible tapeta

As regards the other end of the resonating cavity the existence of a light scattering particle here appears to be still more doubtful

In man a zone of higher refringence at the junction of the outer and inner segments has been described only rather vaguely This higher refringence has been observed only in unstained sections in the optical microscope and only as a zone not a particle This refringent zone is not seen ultrastructurally Of course a refringent zone need not be electron dense On the other hand some change in electron density might be expected It may be the centrosome or densely packed mitochondria lying at this point which have been observed optically as this zone In any case it must be admitted that a coloured light scattering phenomenon has not been observed in this area in contrast to the other end of the resonator It must be concluded therefore that the optical effect cannot be described as being equal at each end

The kind of resonating cavity described by Bulow consequently appears to be in doubt If resonance takes place this may rather be within the membrane systems of the photoreceptor

How can this hypothesis explain the fact that colour blind persons have a normal pigment epithelium and that albinos are not colour blind? It is not sufficient to state that albinos have a membrane delimited structure in the cytoplasm of their pigment epithelium instead of a melanosome and that this can function as a scattering particle because such structures of the same size and membrane delimitation are found in

several places in the cell Resonance might therefore take place from many other organelles Mor over why should the granules be melanized if empty particles were sufficient?

If the resonator hypothesis were accepted in cone vision a fundamentally differert receptor system in the rods must be accepted as no basis for a resonating cavity is found here This seems rather inconsistent from the viewpoint of Nature and hardly probable from an evolutionary point of view

The anatomical basis of the published hypothesis is not rendered probable still less substantiated nor are there proposals for experiments which might lead to confir mation or weakening of the hypothesis

As already said anatomical evidence suggests many facts that reject the asserted hypothesis Some hypothesized physiological events will be discussed in the following

Numerous colour vision theories have been advanced in the past and the theories may in general be classified as in the tradition of either *Thomas Young* or *Ewald Hering* Neither of these main theories can fully explain all experimental facts A conjunction of the two theories which places some emphasis on the colour coding at a level distal to receptors now seems to be the fashion

Any serious colour theory must pay regard to some simple physical observations which were established empirically without physiological reasoning What was later called Grasmann s law says that any pectral colour can be represented mathematically as equivalent to a mixture of three primaries This fundamental law was Young s inspiration when he suggested that the easiest way to explain the tri chromaticity of colour vision was to assume three specific retinal elements each of them sensitive to one of three principal colours Further evidence shows that the hue of all *coloured* objects is one of four pure primal variants red green yellow and blue some of them can be m xed with each other others are incompatible *with one another* Red and green oppose each other (there is no such hue as reddish green) but red can for instance appear in a mixture with yellow or blue This evidence gave rise to *Hern g s ideas* Ultimately any colour theory must account for the fact that for every *colour there* can be found another colour which if mixed with it in the right pro port ons gives white or grey

We are still left with many problems when we seek an exhaustive explanation of *colour vision* Bulow s paper does not however provide us with much new in *formation to clarify* unsolved problems since resonator theories are not new *Stiles* and *E o h first took* up and improved a long established theory *Barer Toraldo di Fr ncia Jean* and *O Brien* and *Myers* have also d scussed the problem and have sug gested *arious structures* as the sources of interference. Up to the present nobody has d n ed *the existence* or uselessness of visual pigments To us it seems meaningless to *question the need* for these pigments or to d scuss other possibilities of energy t ansfer w thout any background in electrophysiological research

The e is no space here to discuss all the *physiological concepts* of the paper but ome points sl ould be mentioned We are not able to predict from the formulae how lecti e is the filtering function of the *supposed resonators* or how narrow are the pectral bands we are talking about Information as to the variation in the dimensions *of cones* s a prerequis te to calculat on *Histology* can only tell us that foveal cones re slender and long compared with the cones of the periphery A systematic variation of the ze cannot be the substrate *of colour* discrimination, since such an assumption, ccord ng to the theory would *apply* a periodical variation of colour sensitivity

throughout the visual field Lacking facts as to the number of specific receptor types presumed to be the outcome of the proposed resonator hypothesis we are able to draw no conclusions as to the validity of the hypothesis as an instrument to explain *Grasmann's* law the four primaries or how the sensation of white is evoked

The Bulowian theory considers the outer segments of the cones as hollow cavities. Their laminated structure is mentioned but not taken into account in calculations. If *Sjostrand's* concepts are valid these membranes are the vehicles of integrated absorption of light quanta and this will cause Bulow's calculations to become out of scale *Moreover these membranes represent discontinuities as regards refractions* of light Furthermore the author a supporter of Stiles wave guide theory does not take into account the fact that the stipulated internal reflection within a retinal cone even with normal incidence of rays must extend into the optic pathway It is also difficult to understand how stored energy (whatever that is) can produce both positive and negative after images and the same phenomenon can give rise to flicker fusion which is commonly believed to have no relation to after images The author claims that the array of isopters for coloured light in the visual field supports his theory but this pattern can just as well be explained by a successive disappearance of colour specific receptors in the retinal periphery *Walraven* interpreted the Stiles Crawford effect of second order as interactions among neurons and *Granit* and *de Valois* obtained their recordings from ganglion cells and not from receptors

In conclusion it must be said that in our opinion sound scientific reasoning consists in the establishment of a working hypothesis but also in an attempt to prove or disprove its consequence by experiment

Niels Bulow You agree with me in the essential points (1) that light is scattered by pigment epithelium granules (2) that the living organism can produce pigment granules which are 5–10 times smaller (in diameter) than the granules in the retina (3) that the intensity of scattered light is proportional to the square of the volume of the granule (4) that the pigment granules in the retina are situated in the microenvironment of the photoreceptors (5) that *Polyak* and *Duke Elder* point out that light is scattered at the junction of the inner and outer segments of the cones (6) that the outer segment of the cones may act as a waveguide and (7) that further experiments are required

The concept that scattering of light by pigment granules situated in close relation to the photoreceptors may protect the photoreceptors against scattered light is something I do not understand

The observed movements of pigment granules inside the cells are influenced by light

Whether the light scattering granule of the cones is a zene or a sphere is of minor interest because light scattering by small particles does not depend on the shape of the particle If this structure is a little larger than the particles which give rise to Rayleigh scattering the consequence is that the intensity of the scattered light is not equal in all directions but enhanced in the direction of the incident light

Albinos have normal premelanosomes (unmelanized pigment granules which are not similar to other organelles) In consequence the intensity of the scattered *light may* be lower but the system is not different in principle An absorption maximum is related to anomalous dispersion and a very high refractive index

The concept that Nature may not operate with two highly different types of photo receptors compares well with the resonator theory If a photoreceptor has a light

scattering granule at the junction of the inner and outer segments standing light waves of certain pecific wavelengths are set up inside the outer segment If a photo recei tor does not have this light scattering structure no standing waves are produced

No physical observations contradict the resonator theory The old phrase Any serious theory of colour vision is worthless if you can obtain an answer by meas uring the length difference between cone outer segments

If the length or the diameter of the outer segment of the cones are plotted in a diagram in relation to their topographical position in the retina curves significant of normal biological variation will be obtained This is in fact the only thing we know about the difference between cones and when applied to the proposed model of a cone this factor explains a number of closely associated physiological phenomena All other theories imply a number of hypothetical interpretations without any common feature

Refraction of light by the internal structure of the outer segment of the cones does not affect the proposed resonator theory because standing light waves are pro duced by two contra directed wave motions Reflection of light by the waveguide is taken into account by the factor cos a Absorption of light is discussed in the original paper

The resonator theory does not deny the photochemical function of visual pigments It is only pointed out that the presence of three different visual pigments in the cones is not necessary in order to explain wavelength discrimination.

The duration of after images in relation to the stimulus energy (*Alpern & Barr* 196? J Opt Soc Amer 5? 219–?71) and the brightness of after images in relation to dark adaj tion (*Padgham* 19ɔ7 Opt Acta 4 102–197) show only one branched curves The colours of after images of complementary hues are displaced a little away from the centre of the visit le spectrum (*Wilson & Brocklebank* 1955 J Opt Soc Amer 4ɔ ?93–?99) These experiments compare well with the proposed loss of the rod mechanism in after images Rods must participate in colour vision by an addition of white white of a spectral composition corresponding to the spectral sensitivity of the rod

The publication of a working hypothesis which points out an alternative possibility may be of value

O A Jensen *Cyclopia*

Preparations from a 6–7 month foetus with severe malformations were demonstrated This f tus was from a 19 year old primipara weighed 9 g and was ?? cm in length There had been no demonstrable noxae during the pregnancy A chromosom study was not carried out

In addition to the cyclopia there was holoprosencephalia, lumbar kyphosis hypo pla ia of the lungs club feet and diaphragmatic hernia.

The lam na cribrosa and the optic foramina could not be demonstrated in th skull There was only one orbit which was centrally placed

In add tion there was a single upper and lower eyelid but two corneae with ap parently fused tissue in the midline A proboscis was seen above the eye.

ect ns from the eyeball showed synopl thalmia with a common atrophic opti n rve tw colobomatous discs two retinae and two lenses Apart from dysplasti osettes in the retina a total iris col boma was the only pathological finding

Another two cases were demonstrated one shown by Otto Erich Lund of Bon

in the European Ophthalmic Pathology Society in 1968 and the other one by Payne in the Verhoeff Society also in 1968

The paper was concluded by comments on the pathogenesis

S Ry Andersen *Radiotherapy in Diseases of the Eye and Orbit* (Publ in Transaction of the Pacific Coast Oto Ophthalmological Society 1969)

Radiotherapy of diseases of the eye and orbit requires close collaboration between radiotherapists ophthalmologists and ophthalmic pathologists As in all radiotherapy there is a risk of damage to the eye and its surrounding Radiotherapy is used for only a relatively few non neoplastic diseases of the eye such as abnormal corneal vascularization in connection with corneal grafting in rosacea keratitis in recurrent pterygium in Mooren s corneal ulcer and in epithelial invasion of the anterior chamber In cases of tumours radiotherapy on certain indications is excellent e g in palpebral carcinoma and indispensable e g in retinoblastoma Centralization of the radiotherapy of retinoblastoma on an inter Scandinavian level would no doubt improve the results During recent years megavolt therapy has widened the indications for radiotherapy of various orbital tumours In the Ophthalmological Tumour Centre we are at present advising megavolt therapy of embryonic sarcomas in some cases followed by exenteration

M Warburg *Two Years Experience from the Eye Clinic for the Mentally Retarded Copenhagen*

The clinic was established in October 1966 During the first two years 568 patients were examined 32 had a visual acuity of less than 6/60 35 of 6/18–6/60 and 99 considerable visual impairment which however could not be measured

The most common causes of visual impairment were optic atrophy found in 98 cases and excessive myopia which in 23 cases caused marked visual impairment despite correction 140 patients were fitted with spectacles the majority because of hypermetropia

As more rare diseases there were 2 patients with Sturge Weber Krabbe s disease one with the elfin face syndrome one with the 18 ring syndrome one with the cri du chat syndrome and a brother and sister with ptosis and generalized hypotonia

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421st Meeting Dec 7 1968 in Copenhagen
(Eye Clinic Rigshospitalet Blegdamsvej)

BJERRUM LECTURE

T Krakau *Regulation of Ocular Tension* Acta Ophthal 47 (1969) 660

492nd Meeting
Joint Meeting with the Ophthalmological Society of Southern Sweden
(Eye Clinic University Hospital Lund)

S Ry Andersen *Histopathology of Temporal Arteritis* (also publ in Transactions of the Pacific Coast Oto Ophthalmological Society 1969)

Analysis of 93 eyes with ocular giant cell arteritis (of the Horton Magath Brown type) reported in the literature after histopathological study 6 of these eyes had been examined by the author In all cases where the histological examination included the periaxial as well as the axial arterial system both systems were involved by giant cell arteritis or showed the sequelae thereof One quarter of the cases exhibited ischaemic necrosis in a zone of the optic nerve posterior to the lamina cribrosa Necrosis of the disc and total necrosis of the optic nerve was extremely rare. Giant cell arteritis of another type was also found in two cases in the central retinal artery

Giant cell arteritis never affects the retina or choroidal vessels The prophylactic value of long term steroid therapy was stressed

H Bynke *A Case of Carotids Cavernosus Fistula with Contralateral Exophthalmos* Acta Ophthal 48 (1970) 971

J Edmund and O A Jensen *Dietetic Treatment of Malignant Melanoma of the Choroid*

M Warburg *Microphthalmos in Mentally Retarded Persons* (Publ in Birth Defects Original Article Series The Second Conference on the Clinical Delineation of Birth Defects)

Since the publication of Sjogren & Larsson's monograph on microphthalmos and anophthalmos with and without mental retardation (1949) microphthalmos in mentally retarded individuals has generally been considered a disease *sui generis* It was demonstrated that the cases may be divided into well defined genetic chromosomal and teratologic sub groups and that there are moreover a number of less well defined cases in which however the symptoms and signs differ mutually The following is a useful classification (1) genetic types (dominant autosomal recessive and sex linked recessive) (2) chromosomal anomalies (trisomy 13 D_1 ring chromosome deletion of No 13 deletion of the short arm of chromosome 4 and 18 trisomy) (3) syndromes (4) teratological phenocopies and (5) postnatal injuries and infections which give rise to phthisis

V Deyer *Medical Prescription of Contact Lenses* Publ Acta Ophthal 48 (1970) 50

M S Norn and V Frølund Thomsen *Disinfection of Goldmann's Applanation Tonometer Prism by Means of Ultraviolet Light* Acta Ophthal 47 (1969) 1207–1218 The apparatus constructed by us has the disadvantage that the anterior surface of the applanation tonometer prism becomes opaque in the course of a few months so that 3 or 4 prisms are used each year In return it is possible to perform applanation in cases where there is also a suspicion of infection in the eye The disinfection apparatus is of particular importance in the prophylaxis against epidemic keratoconjunctivitis.

Professor Palm has concluded that the increased cost is not prohibitive when considering the object

T Krakau *A Vibration Tonometer*

B Lindner *Three Aids in the Treatment of Retinal Detachment*

423rd Meeting Mar 15 1969 in Copenhagen (Eye Clinic Rigshospitalet Blegdamsvej)

K Norskov *Glaucoma Screening Problems* Critical Evaluation Based on Routine Tonometry Among Members of the Volunteer Donor Corps of the Island of Falster (Denmark) Publ Acta Ophthal 48 (1970) 401

P Brendstrup *Vitreous Haemorrhage in Newborns* Acta Ophthal 47 (1969) 30?

H Fledelius and S E Simonsen *A Family with Bilateral Symmetrical Sectorial Pigmentary Retina Lesion* A Report on Three Cases of the Hereditary Disorder Acta Ophthal 48 (1970) 14

D Riise *Modified Tonography Using Suction Cup*

A suction cup technique has previously been used by Rosengren and Ericson for determining the formation of aqueous humour After an initial rise under the suction cup the tension gradually decreases During recent years there have been several reports on methods intended to measure this decrease.

The curve representing the decrease in tension like the tonography curve expresses the facility of outflow

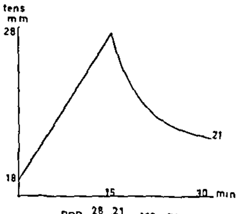


Fig 1

In the suction cup method the decrease in tension is assessed for 15 minutes in relation to the increase in tension which occurred during the 15 min. that the suction cup was attached to the eye (cf. Fig. 1).

Comparison of conventional tonography with the suction cup method was performed in the case of 47 eyes. The results are shown in Table I.

In a number of the cases the rise in tension in the suction cup method was so slight that the values were inapplicable. Since, moreover, the suction cup method is not based upon a tension curve but upon individual tension measurements, the result will be considerably influenced by the standard deviation of ± 2 mm.

It is concluded that the suction cup method hardly possesses advantages that can justify its replacing conventional tonography.

Table I

	Tonography		Suction cup	
Glaucoma (in medication)	Abnormal	16	Abnormal	14
			Normal	2
	Normal	15	Abnormal	10
			Normal	5
Glaucoma obs.	Abnormal	2	Abnormal	2
			Normal	0
	Normal	3	Abnormal	2
			Normal	1
Normal	Abnormal	1	Abnormal	1
			Normal	0
	Normal	10	Abnormal	3
			Normal	7

424th Meeting Apr. 26 and 27, 1969 in Nyborg
Seminar on Geriatric Ophthalmology

O. A. Jensen: *Arteriosclerosis.* General Comments.

O. A. Jensen: *Histopathology in Arteriosclerotic and Degenerative Changes of the Eyeground.*

H. W. Larsen: *Morphology of Senile Fundal Changes.*

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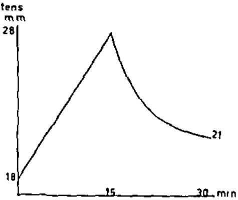


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	Tonography		Suction cup	
Glaucoma (in medication)	Abnormal	16	Abnormal	14
			Normal	2
	Normal	15	Abnormal	10
			Normal	5
Glaucoma obs	Abnormal	9	Abnormal	2
			Normal	0
	Normal	3	Abnormal	2
			Normal	1
Normal	Abnormal	1	Abnormal	1
			Normal	0
	Normal	10	Abnormal	3
			Normal	7

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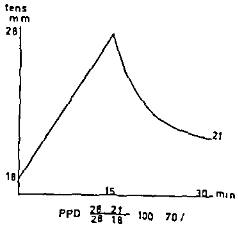


Fig 1

P M Møller and E Goldschmidt *Ocular Tension after Cataract Extraction*

The material comprises 14 males and 18 females with senile cataract who have had uncomplicated cataract extraction All the lenses were extracted by the cryostilette 11 patients were treated with chymotrypsin 25 had air in the chamber at the termi nation of the operation.

Postoperatively the tension was measured daily with the Goldmann applanation tonometer In one case the test could not be performed mainly because the patient was mentally confused

Our primary aim was to ascertain whether the tension among the group treated wi h chymotrypsin during the operation differed from that in the others Since no d fference was found the material was analysed as a whole.

Out of the ?6 patients we have characterized 10 as hypertensive 3 as hypotensive and the remainder as normotensive

An increase in tension during the initial postoperative phase is very common The tension seldom exceeds 30 mm but may rise to about 50 mm with consequent corneal oedema As a rule the tension soon subsides spontaneously and during the sub equent period the operated eye is often hypotensive

The duration of the hypotension may vary but it may persist for several weeks w thout any evidence of fistulation or choroidal detachment

The end result was satisfactory in all cases

S Vedel Kessing and K Holm *Changes of Ageing in the Conjunctival Epi thelium*

N Ehlers *Non pathological Age Changes in the Cornea* It may be difficult to delineate the period of life in which corneal changes occur Genetic factors play a decisive role concerning the time of their onset and their development The incidence of patholog cal changes increases with advancing age Such changes may be the sequelae of past infections or injuries or they may represent the large group of dystrophic degenerative states which may manifest themselves at any age All such pathological changes cannot be included as age conditioned or senile changes which must be taken to mean exclusively those which are due only to age

In the literature on age conditioned corneal changes there is little or no sys tematism These changes are listed in Table I

Table I

Non pathological age changes in the cornea

Involutions	Peripheral changes	Central changes
Changed curvature	Arcus senil s	Smoky (cloudy) degeneration
Changed thickness	White limb us girdle	Mosaic degenerat on
Reduced sens bil ty	Sclerosis of limbal vessels	Posterior crocodile shagreen
Reduced tempe atur	Dellen of Fuchs	Cornea farinata
Increased gloss	Hassall Henle bodies	Hudson Stahli s line
Reduced metabol sm	Deg spherularis elaioides	

M Warburg *Differential Diagnoses in Senile Macular Degeneration*

B Moestrup *Ocular Age conditioned Changes in a Geriatric Material*

P Brændstrup *Glaucoma Simplex*

E Goldschmidt *The Heredity of Adult Glaucoma*

It is well known that the various clinical types of glaucoma may be familial but this is not tantamount to their being of genetic origin Critical perusal of the literature shows no evidence that glaucoma in the elderly is as a general rule of a genetic nature whereas genetic factors are presumably more often operative in younger individuals In most published families the affected members have had the same type of glaucoma but there are also numerous examples of different clinical types in the same family

It remains entirely unelucidated whether genetic factors are of particular importance in open angle glaucoma closed angle glaucoma pigment glaucoma or capsular glaucoma There have been no serial studies of glaucoma in twins

During recent years a number of valuable data on the genetic constitution of patients with glaucoma have been accumulated It must be considered a proven fact that many but not all give a positive reaction to local steroid therapy Moreover there is a larger number of PCT non tasters among patients with glaucoma than in the general population

However neither steroid tests nor PTC test can be used for detecting early cases of glaucoma It is concluded that today there are no genetic properties which bear an unambiguous relation to glaucoma

H Skydsgaard *On Special Optic Aids for the Elderly*

I Krarup Jensen *The Practical Procedure in Prescribing Optic Aids*

S E Lorentzen *Occlusion of the Central Retinal Artery* A Follow up Study Publ Acta Ophthal *47* (1969) 690

M S Norn *Temporal Arteritis*

We are dealing with a disease in elderly people for which we have a really effective and important treatment It is striking to watch the rapid effect Old grey despairing people who on the very next day give an impression of being *rejuvenated* optimistic and often relieved of severe pain The main effect of treatment is preservation of vision in the remaining eye The treatment and follow up often takes years and in some cases is life long

It is the ophthalmologist s duty to hospitalize the suspicious cases often the despairing patients who would rather wait until tomorrow or stay at home but this may cost them the vision in the other eye

Reference

M S Norn (1966) *Ugeskrift f Læger 128 532–537*

H H Seedorff *Indication for Cataract Operation – with a Particular View to Working Elderly Persons*

V Dreyer *Contact Lens Therapy of Aphakia in the Elderly* (Publ with H H Seedorff in *Ugeskrift f Læger)*

Wise George N Dollery Colin T & Henkind Paul The retinal circulation 576 pages 678 illustrations Harper & Row New York 1971 Cloth bound Price $ 35

This interesting book deals with the clinical pharmacological physiological and experimental aspects of retinal and choroidal circulation and includes chapters on development of retinal vessels pattern and structure of retinal vessels papillary angio architecture retinal vessels in selected animals (pig rabbit horse cat and dog) fluorescein angiography microscopic features studied in ordinary and in retinal digest preparations diseases in arterial insufficiency capillary and venous insufficiency hypertensive retinopathy diabetic retinopathy disciform macular diseases and experimental diseases

The book is written by well known authorities in this field with comments based on their own investigations including hitherto unpublished observations

The book is up to date with interesting comments regarding retrolental fibroplasia, the role of choroidal oxygen on the retinal circulation, development of macular degeneration and serous central retinopathy indications of photocoagulation in diabetic retinopathy etc

Of great interest is a critical evaluation of vasodilator drugs and their possible effect on the retinal blood flow

The following Scandinavian authors are quoted E. Palm (blood retinal barrière) G Karpe (ERG) S E Simonsen (abnormal oscillotony potentials even before visible diabetic retinopathy) P M Møller and I M Haar (periphlebitis retinae in association with multiple sclerosis) P Brændstrup (haemorrhagic glaucoma in relation to central retinal vein thrombosis) S Hanum P H Madsen, V A Jensen K Lundbæck H W Larsen (diabetic angiopathy) Mette Warburg (Norries disease) E Linnér (photo coagulation) J Fahmy (intraocular haemorrhage following subarachnoid haemorrhage) among others

It is a splendid book with interesting black and white photos of retina with and without fluorescein, of histologic preparations and of electronmicrographs and contains schematic drawings as well

This book is to be recommended *M S Norn*

Von Noorden Gunter K & Maumenee A Eduard Atlas of Strabismus Verlag F K Schattauer Stuttgart – New York 1971 183 pages 114 figures Price DM 88

This book represents the German translation of the author's well known original edition of 1967 Atlas of Strabismus

Let it first be stated that the book is one of the best purchases ophthalmologists and specialists in orthoptics can make if they want clear concise and quick guidance on the practical diagnostic problems presented by their strabismic patients

The format of this German edition is handier than its American predecessor to which it otherwise for all practical purposes is identical

The book distinguishes itself by abundant exemplary instructive illustrations (figures and photographs) and a matching extremely concise and didactic text The work can be recommended absolutely as one of the best and most easily comprehended textbooks on the many practical problems of diagnosing strabismus

E Gregersen

The causes of these changes are on the whole, unknown Future geriatric research will perhaps afford the answer as to whether they are due to vascular obliterations, denaturation of protein enzyme inactivation or something else.

J Edmund *Keratoplasty in Patients with Senile Corneal Dystrophy*

From the Eye Department
(Heads P Brændstrup M S Norn & K Norskov)
Kommunehospitalet Copenhagen Denmark

TETRAZOLIUM – ALCIAN BLUE MIXTURE

I Vital Staining of Cornea and Conjunctiva

BY

M S NORN

A mixture of 1% iodonitrotetrazolium and 1/4% alcian blue effects specific vital staining of the cornea and conjunctiva with enzyme containing degenerate cells assuming a red colour and mucus a blue
The investigation comprised 307 eyes
The double staining showed that mucus does not tend to become deposited on the surface of degenerate cells that are still alive enough to possess enzymatic activity
Punctate red staining of the tarsal conjunctiva is a characteristic feature of *chronic simple conjunctivitis* (inferior tarsus stained in 37% superior tarsus in 50% altogether in 60% of eyes)
In *keratoconjunctivitis sicca* we find not only mucus and degenerate cells in the exposed sections of the cornea and the bulbar conjunctiva but also degenerate cells with enzymatic activity on the tarsal conjunctiva
Staining in other conditions is described and the conclusion is drawn that this specific vitalstain mixture is *indicated* in conjunctivitis and other conjunctival disorders but *contra indicated* in cases of lesions not covered by epithelium

Key words vital staining – cornea – conjunctiva – tetrazolium – iodonitrotetrazolium – alcian blue – chronic simple conjunctivitis

Received February 15 197?

Neuro-Ophthalmology Course Bascom Palmer Eye Institute University of Miami

The Bascom Palmer Eye Institute Department of Ophthalmology University of Miami will conduct the annual Neuro Ophthalmology Course January 3–6 1973 The meeting will be held at the new Sonesta Beach Hotel Key Biscayne (Miami) Florida The faculty will include Stuart B Brown Ronald Burde Robert F Cullen Robert B Daroff Noble J David John T Flynn Donald M Gass Joel S Glaser William F Hoyt Simmons Lessell Martin Lubow Edward W Norton Larry K Page Hubert L Rosomoff Norman J Schatz J Lawton Smith B Todd Troost

The Course is designed to present basic and clinical material in Neuro Ophthalmology Neurology and Neuro Surgery Major topics include I Diseases of the Optic Nerve II Disorders of Ocular Motility III Neuro Ophthalmology of Infancy and Childhood

For further information or requests for registration contact Dr Joel S Glaser Neuro Ophthalmology Course 1638 N W 10th Avenue Miami Florida 33136

then plotted in a graph The degree of staining in the different regions is rendered in arbitrary grades from 1 to 5 (grade 3 representing moderate staining grade 4 considerable grade 5 maximum grade 2 weak and grade 1 minimum)

Material

A total of 307 eyes were examined The diagnoses are shown in Table I

Other disorders comprise papillomatous conjunctivitis follicular conjunctivitis blepharitis meibomitis eczema of eyelids *exophthalmos glaucoma* epiphora pemphigus dacryocystitis cataract extracted eyes within 4 weeks of operation and a group under observation

Result

Fig 1 shows the average staining grade in the total clinical material comprising the individual regions

Degenerate enzyme containing cells predominated on cornea and inferior and superior tarsal conjunctivae while mucus predominated on plica semilunaris caruncle and especially over the area of Marx line (the region just behind the margins of the upper and lower lids)

The investigation showed that red and blue colours may occur quite independently e g red colouring of a keratitic process without mucous patchings and punctate bluish green colouring alone of mucus along Marx line

Normal Eyes

Enzyme containing cells were *not* found on the cornea nor on the tarsus and only in one case on the bulbar conjunctiva Marx line and on the caruncle

Punctate staining of mucus on the other hand was seen in several normal eyes especially on the bulbar conjunctiva and Marx line along the lower and upper lids (Table I)

Corneal Disorders

In cases of active keratitis considerable numbers of enzyme containing cells were usually found on the corneal process in some instances with minor

In a previous study I demonstrated that alcian blue can be used as a specific vital stain in the conjunctival sac mucus assuming a bluish green colour (Norn 1963 1964)

Another investigation disclosed that the colourless compound iodonitrotetrazolium stains degenerate enzyme containing cells on the conjunctiva and cornea a red colour within four minutes (Norn 1971)

The substance penetrates into the degenerate cell and becomes reduced by enzymes to red formazan granules in the cytoplasm of the cell

Experiments have shown that the two substances can be mixed and that the mixture is stable and useful as a specific double vital stain

Using a mixture of the two substances has the following advantages just one instillation is sufficient and a correct concentration ratio between the two substances can easily be obtained

Blue areas represent mucus and red areas indicate degenerate cells which are still alive as is evidenced by preserved enzymatic activity Thus quantitative proportions of mucus and enzyme containing cells can be established definitely

The object of the present investigation was to study the proportion of mucus to enzyme containing cells on the cornea and the conjunctiva by vital staining of a clinical material

Methods

The vital stain mixture employed has the following formula

iodonitrotetrazolium	100 mg
alcian blue	25 mg
phenylmercurinitrate	0 1 mg
distilled water to	10 g
aseptically prepared	

The mixture contains 1 % tetrazolium but only 1/4 % alcian blue Previously I instilled a 1 % concentration of alcian blue when staining with this dye separately

From a pipette bottle mounted with a steristar needle (luminal diameter 0 5 mm) one drop (10 μl) of the dye mixture is dropped on to the superior temporal part of the bulbar conjunctiva while the patient is looking down and nasally The vital staining result is read in the slit lamp between not less than 4 minutes and not more than 10 minutes after the instillation and

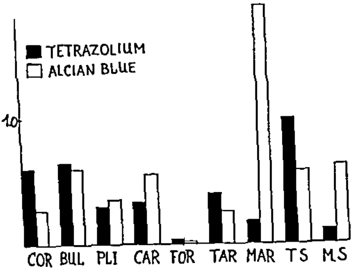


Fig 1

Vital staining of 307 eyes with tetrazolium – alcian blue mixture in different regions Black columns 1 % tetrazolium white columns 1/4 % alcian blue. Abscissa nine different regions Ordinate colour grade (arbitrary grading 1–5)

mucous patchings In one case mucus alone was seen This was a case of dendritic keratitis about to heal up A red stained conjunctiva was never noticed but green mucous patchings as in normal eyes were found in some cases

In *marginal* keratitis red foci were observed on the cornea Mucous patchings were here found only around or on some of these foci

Where foreign bodies had been removed with a drill the entire base of the corneal ulcer was red with scattered mucous patchings in the concavity and along the edge

Keratoconjunctivitis Sicca

The exposed parts of the cornea and conjunctiva were found to be stained by alcian blue in the same characteristic manner as noticed after staining with rose bengal This indicated presence not only of degenerate and dead cells (stained with rose bengal) but also of mucous patchings within the exposed desiccated area (stained with alcian blue)

Tetrazolium stained more intensely in the same regions In addition staining

Table I

Tetrazolium - alcian blue vital staining of cornea and conjunctiva The figures indicate the percentage numbers of eyes stained by tetrazolium (T) and by alcian blue (A) in the region concerned

	No	Cornea		Bulb conj		Tarsus inf		Marx inf		Tarsus sup		Marx sup	
		T	A	T	A	T	A	T	A	T	A	T	A
normal eyes	23	0	0	4	26	0	4	4	56	0	4	0	26
corneal disorders	10	90	100	0	10	0	10	0	30	10	10	0	10
keratoconjunc sicca	6	100	100	100	100	83	50	33	100	83	17	50	33
simple chron conj	48	13	0	29	23	37	19	8	52	50	29	4	35
contact lens wearers	18	0	6	44	26	6	6	6	56	6	16	11	17
others	154	12	4	8	12	5	3	3	49	18	15	2	15
Total	307	15	8	15	18	11	7	6	47	21	17	4	21

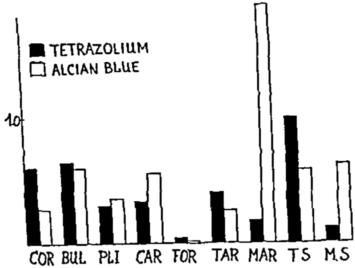


Fig 1

Vital staining of 30 eyes with tetrazolium – alcian blue mixture in different regions Black columns 1 % tetrazolium white columns 1/4 % alcian blue. Abscissa nine different regions Ordinate colour grade (arbitrary grading 1–5)

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Tetrazolium stained more intensely in the same regions In addition staining

was seen of the inferior and superior tarsi in the form of punctate staining of a broad area along most of the lid margin behind Marx line

This was an interesting observation because it showed that it is not only the epithelium exposed to air that becomes affected in *keratoconjunctivitis sicca* but also that of the tarsal conjunctiva. The former region is stained by rose bengal, alcian blue and tetrazolium, the latter usually only by tetrazolium. The non exposed tarsal epithelium thus contains degenerate cells with enzymatic activity, but only rarely contains dead cells or mucus

Chronic Simple Conjunctivitis

This is a condition characterized by persistent considerable conjunctival complaints without associated objective signs

Punctate red staining was a surprisingly frequent finding on the superior (50 %) or the inferior (37 %) tarsal conjunctiva, in 60 % present in at least one of these areas. Compared with the normal material the difference was statistically significant ($p < 0.01$)

The staining manifested itself as small red dots in a broad band behind Marx line extending over at most half of the breadth of the lid, most often localized in the central region, more rarely medially and most rarely laterally

In some instances red dots were found also medially on the bulbar conjunctiva, more rarely on the caruncle. However the latter findings did not differ significantly from those in the remaining material

Mucus was not present in larger amounts than in normals. Often a green Marx line was seen behind which on the tarsus a red band of enzyme containing cells appeared. Microscopy of the red dots on the tarsal conjunctiva showed them to consist of nests of cylindric epithelial cells with red granules in the cytoplasm

The red staining on the tarsal conjunctiva is characteristic of chronic simple conjunctivitis. It is easily distinguishable from the finding in keratoconjunctivitis sicca where the exposed parts of the cornea and the bulbar conjunctiva are stained also

Mucus was rarely seen on the red stained tarsal conjunctiva

Contact Lens Wearers

The eyes of several corneal contact lens wearers show a crescent shaped rose bengal stained line on the bulbar conjunctiva indicating pressure by the lower edge of the lens

Using a tetrazolium – alcian blue mixture a similar crescent shaped line was

noticed in 10 out of 18 contact lens wearers The line most often consisted of degenerate cells more rarely of mucus

Only one patient had chronic conjunctival complaints This was the only case presenting red punctate staining of the tarsus as in simple conjunctivitis

Infectious Conjunctivitis

Among 24 patients with acute bacterial conjunctivitis and among 22 patients with protracted bacterial conjunctivitis only four presented red staining of the cornea This colouring was in one case interpretable as traces left after a foreign body and in the others as signs of bacteria beginning to spread to the cornea Mucus and cells on the conjunctiva stained as in normal eyes whereas the mucous thread in the inferior conjunctival fornix did not

In normal sterile cases the mucous thread assumed a mainly blue colour (mucus) In bacterial conjunctivitis it became mainly red (enzyme containing degenerate neutrophilic leucocytes)

This important finding will be dealt with in greater detail in a future paper

Other Disorders

Among 19 patients with papillomatous conjunctivitis five were found to have net like mucous patchings on the superior tarsus the meshes of which enclosed the papillae No red staining of the epithelium was seen

Immediately after corrosion by $^1/_2$ % silver nitrate ($AgNO_3$) pronounced punctate red staining was in some cases seen over the entire cornea and conjunctiva whereas no colouring of mucus was observed In other cases minimum or no staining occurred

Tonometry was in some instances followed by red staining of the cornea but no staining of mucus

After intense rubbing of the eye with the lid closed moderate red staining was in some cases observed on the cornea and the bulbar and tarsal conjunctivae In other cases even very intense rubbing caused no staining

A total of 69 *cataract extracted* patients were examined less than *four weeks* after the extraction In seven the cornea was seen to be stained Among these there was one case with evidence of keratoconjunctivitis sicca and one case of Dellen

The bottom of the corneal excavation (Dellen) presented inferiorly a red stained band of epithelial cells while along the upper edge several blue mucous flakes were seen

The inferior tarsus was red stained in one case only (obs for keratocon

junctivitis sicca) The superior tarsus was not examined on cataract extracted patients as this might damage the eye

A group of 29 cases were characterized as cases under observation Of these two presented red-staining of the inferior tarsal conjunctiva and six of the superior tarsal conjunctiva findings which bore out the suspected diagnoses of chronic simple conjunctivitis

In 47 % of lower lids and 21 % of upper lids in the total material Marx line was covered by mucus Scanty red colouring was seen in few cases only (in 6 and 4 % respectively) Red staining was found particularly in cases of bacterial conjunctivitis and meibomitis

Discussion

The results of the present study of vital staining with a mixture of tetrazolium and alcian blue bore out the observation made previously by using the two dyes separately (iodonitrotetrazolium (Norn 1971) alcian blue (Norn 1963 1964))

The investigation further demonstrated the proportions of the regions containing degenerate cells with enzymatic activity (tetrazolium stained) to those covered by mucus (alcian blue stained)

Marx line is the term originally employed for the line behind the ciliary margin which becomes stained by rose bengal i e contains degenerate and dead nucleated squamous cells The present investigation showed that the region often is covered by large amounts of punctate mucous patchings but only in rare cases does it contain degenerate epithelial cells with enzymatic activity In keratoconjunctivitis sicca we find not only the characteristic desiccation of exposed cornea and conjunctiva but also nests of enzyme containing cells on the tarsal conjunctiva which rarely is covered by mucus

Mucus tends to become deposited on uneven corneal and conjunctival surface areas in grooves on sutures (Norn 1972a) and on dead cells The double staining showed that mucus very rarely covers degenerate cells which still are sufficiently alive as to possess enzymatic activity

This investigation further established that a characteristic red staining may be seen on the inferior tarsus in chronic simple conjunctivitis The phenomenon was also shown to be even more frequent on the superior tarsus and not to be accompanied by mucous patchings

The phenomenon might conceivably depend on age It has however also been observed in relatively young persons (in one out of six aged under 60)

and found to be absent in normal elderly individuals (in a total of eight sub jects aged over 70)

A study comprising patients with simple conjunctivitis subjected to repeated vital stainings over a period of months is in preparation

The phenomenon is not due to simple rubbing because this would also provoke vital staining elsewhere e g on the cornea

The above vital stain mixture is contra indicated in cases of lesions that are not covered by epithelium because alcian blue may cause permanent staining of connective tissue This rule of contra indication having been complied with however no such tatooing was seen in the material under review

The tetrazolium – alcian blue mixture is indicated in the presence of con junctival complaints because this can confirm a diagnosis of simple conjunc tivitis and because the colour of the mucous thread can elucidate whether the conjunctiva is sterile or whether bacterial infectious conjunctivitis is present The latter question will be dealt with in a future paper

On the other hand the tetrazolium – alcian blue mixture is *contra indicated* in the presence of corrosions and deep keratitis In such conditions and in contact lens wearers vital staining with a mixture of rose bengal and fluores cein is preferable though the information obtained with this mixture is quite different fluorescein stains epithelial defects and rose bengal degenerate cells dead cells and mucus (Norn 1972b)

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TETRAZOLIUM – ALCIAN BLUE MIXTURE
II Vital Staining of Mucous Thread in Inferior Conjunctival Fornix

BY

M S NORN

The mucous thread in the inferior conjunctival fornix is vital stained specifically by a mixture of 1 % tetrazolium and 1/4 % alcian blue
A total of 307 eyes were examined in the slit lamp and *101* of the vital stained mucous threads were microscoped and measured
Predominantly red staining of the mucous thread was found to indicate bacterial infectious conjunctivitis and predominantly green staining indicated a sterile conjunctiva
The predominantly red staining in infectious conjunctivitis is due to myriads of enzyme containing degenerate neutrophilic leucocytes while the green colour comes from mucous fibrils
In normal eyes the mucous thread comprises on an average 3 1 mm² mucus 1 5 mm² vacuoles and 0 02 mm red areas For acute infectious conjunctivitis the corresponding figures are 3 5 1 0 and 20 8 mm and for chronic infectious conjunctivitis 1 9 0 4 and 29 0 mm
The tetrazolium alcian blue mixture is *indicated* in cases of conjunctival complaints (establishes diagnoses of infectious conjunctivitis and chronic simple *conjunctivitis*) *but is contraindicated in the presence of* lesions that are not covered by epithelium

Key words vital staining – tetrazolium – alcian blue – bacterial infectious conjunctivitis – the mucous thread in the infections conjunctival fornix

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A mixture of tetrazolium and alcian blue is useful for vital staining of cornea and conjunctiva because the mixture is stable and because the two components of the mixture *preserve their specific staining* properties

Alcian blue stains mucus a greenish blue colour

Tetrazolium as such is colourless but becomes converted to formazan by reduction Enzyme containing degenerate cells and enzyme containing detritus therefore take a red stain

In a previous paper (Norn 1972c) the observation is mentioned that keratitis affected corneal tissue is stained red with scattered blue mucous patchings Intense staining is seen in keratoconjunctivitis sicca In simple chronic con junctivitis the superior or the inferior tarsal conjunctiva presents punctate red staining

The mucous thread in the inferior conjunctival fornix likewise becomes stained by this mixture in some cases mainly greenish blue, in others mainly red

The object of the present study was to throw light on the stainability of the mucous thread in different clinical states assessed partly by examination in the slit lamp and partly by microscopy

Method and Material

The vital stain mixture used is composed as follows

iodonitrotetrazolium	100 mg
alcian blue	25 mg
phenylmercuric nitrate	0 1 mg
distilled water to	10 g
aseptically prepared	

One drop of this mixture (10 μl) was applied on the upper lateral part of the bulbar conjunctiva After 4–10 minutes the colour of the mucous thread was studied in the slit lamp

The method is described in detail *in the previous paper* (Norn 1972c)

The series of cases is identical with that described in the above paper and comprises a total of 307 eyes

RESULT

A mucous thread was found in the inferior conjunctival fornix of all the eyes *In some* eyes the mucous thread extended through the entire length of the inferior fornix while in others blinking caused it to move medially towards

the inner canthus In one case only (conjunctival pemphigus) was it rudimentary

The mucous thread was most often mainly green with few, scattered red granules In other cases it was mainly red, seen as big red lumps surrounded by smaller, green fibres In no more than 10 % was it green throughout A totally red mucous thread was never observed

The results of the investigation have been set out in Table I

In normal eyes the mucous thread is predominantly green i e it consists of mucopolysaccharide containing mucous fibrils

In acute and chronic infectious conjunctivitis the red colour predominates or the red areas are equal in size to the green

The red parts consist of myriads of degenerate enzyme containing neutrophilic leucocytes

This dye mixture thus allows us to decide whether the conjunctiva is bacterially infected or sterile

If the mucous thread is mainly green the conjunctiva is sterile

If red predominates or if the red areas are judged to be equal in size to the green the conjunctiva is bacterially infected

This method gave a *false negative* result in 3 % (one out of 32 with acute or chronic infectious conjunctivitis presented a predominantly green mucous thread) and a *false positive* result in 13 % (in three out of 23 normal eyes red and green were equally represented Microscopy showed red vacuoles but no neutrophilic leucocytes)

Table I

The mucous thread in the inf conjunctival fornix assessed in the slit lamp after vital *staining with the tetrazolium – alcian blue mixture*

	red>green	red=green	red<green	number
Normal eyes	9	4	87	23
Acute infect conj	75	25	0	24
Chron infect conj	64	31	5	22
C L	5	0	95	19
Cataract < 4 weeks	18	15	67	68
Meibomitis	80	20	0	5
Observation	14	28	58	29
Chron simple conj	8	10	82	48
Total	23	14	62	307

In the *normal* eyes the red dots seen in the predominantly green mucous thread were found either evenly distributed as fine red granules over the entire green mucous thread or accumulated in small groups The majority of such groups were localized medially

Desiccated sleepy seeds on the skin at the inner canthus were seen to be yellow or white Sleepy seeds were not included in the assessment of the mucous thread

In *infectious conjunctivitis* large red lumps of pus were in most cases found scattered along the entire length of the inferior fornix A few thin mucous fibres were in some instances noticed at the periphery of the pus lumps occasionally connecting such lumps

In a small number of eyes (five) a large red lump of mucus was seen medially in the inferior fornix while the lateral section of the mucous thread was thin and green The red area exceeded the green in size

Among *contact lens wearers* with no clinical signs of infection one unexpectedly displayed signs of bacterial infection

Among *cataract extracted* patients 33% showed infection This finding was independent of the interval after the operation the eyes having been examined up to four weeks after The earliest examinations were made 48 hours after the operation when the mechanical injury and the consequently released neutrophilia evidently had subsided the mucous thread being mainly green Infected cases were found evenly distributed in the series

Possible presence of pus in mucous threads enveloping conjunctival or corneoscleral sutures has been reported in a previous paper (Norn 1972a)

In the group with *keratoconjunctivitis sicca* the mucous thread was predominantly green in three cases and predominantly red in three others Microscopy disclosed that in these cases the red regions were not due to neutrophilic leucocytes but to red vacuoles and red granules (see later)

Among the patients with *simple conjunctivitis* unexpected signs of infectious conjunctivitis were present in 19%

Corrosion by silver nitrate and hydrochloric acid was seen to provoke a predominantly red mucous thread Minor mechanical injuries on the other hand (such as tonometry rubbing diagnostic contact lens examination) caused no alteration of the normal predominantly green mucous thread

Valuable diagnostic information was obtained in 29 clinically doubtful cases

In the following states bacterial infection could be left out of account the mucous thread being mainly green *prior to* cataract extraction, conjunctivitis treated for a long time with different antibiotics unilateral *conjunctivitis* observations for infectious conjunctivitis

In the following states a red mucous thread was found indicating presence of bacterial infectious conjunctivitis obs for iritis chemosis prior to cataract extraction, contralateral eye with infectious conjunctivitis simple conjunctivitis with concurrent suspicion of infectious conjunctivitis

Microscopy

In 101 cases the vital stained mucous thread in the inferior conjunctival fornix after having been inspected in the slit lamp was transferred to a slide and subjected to microscopy

PROCEDURE

The vital stained mucous thread is touched at one end by a small wooden stick (a toothpick) The toothpick with the adhering mucous thread is then raised cautiously from the conjunctiva Another toothpick is brought into contact with the other end of the mucous thread which likewise is raised from the *conjunctival base The whole mucous thread can then be lifted* carefully out of the conjunctiva and transferred between the two toothpicks to a slide on which it is spread care being taken not to rupture it The slide with the mucous thread is kept in a moist chamber (a vial containing moist cotton closed by a tight fitting plastic lid) Microscopy is carried out after a few hours following application of a drop of saline and covering by a cover slip The cell content of the mucous thread is recorded The extent of green areas and different types of red areas are measured by means of a net ocular

Results

The mucous thread was divided into the following areas

I Green areas consisting of alcian blue stained mucous fibrils occasionally with few scattered most often epithelial cells

II Red areas consisting of closely packed neutrophilic leucocytes These may present a diffuse weak red colour or they may contain intensely red granules in their cytoplasm

III Yellowish red vacuoles (Norn 1968) i e large diffusely stained round or oval amorphous formations found scattered in the mucous thread with a tendency towards accumulation nasally They consist of enzyme containing cell detritus and foreign bodies

IV Fine red granules in great numbers adhering to mucous fibrils

Green areas (I) predominate in the normal sterile conjunctiva The small scattered red dots in the normal conjunctiva are vacuoles (III) Bacterial infectious conjunctivitis on the other hand is characterized by myriads of red neutrophilic leucocytes (II)

The results of the area measurements are shown in Table II

In normal eyes the green mucous area averaged 3 14 mm while a smaller area (1 25 mm²) presented vacuoles A small region with neutrophilic leucocytes was seen in one case only In the other cases only few scattered mainly epithelial cells were found but no red areas with either cells or red granules

In acute and chronic *infectious conjunctivitis* on the other hand red areas predominated consisting of myriads of neutrophilic leucocytes The difference from the normal series is significant ($p < 0\,001$)

The amount of mucus was found to be relatively smaller than in the normal eyes but the absolute amount was not definitely reduced in infectious conjunctivitis compared with the normal series

In *chronic simple conjunctivitis* the amount of mucus was perhaps slightly increased ($p < 0\,02$) but the conditions were otherwise as in normal eyes

In *blepharoconjunctivitis* cases and in contact lens wearers no difference was noticed from the conditions in normal eyes

Regarding *keratoconjunctivitis sicca* four eyes presented on an average

Table II

Microscopy of the tetrazolium – alcian blue stained mucous thread Areas of mucus vacuoles and red areas with neutrophilic leucocytes in mm and standard error of mean.

	mucus	vacuoles	red areas	number
Normal eyes	3 1±0 7	1.5±0.5	0 0?±0 16	19
Acute infect conj	3.5±1 1	1 0±1 4	20 8 ±5 1	9
Chron. infect conj	1.9±0.5	0 4±0.3	29 0 ±5.9	14
Chron simple conj	6 7±1 1	2 2±0.5	0	14
Blepharocon junct vitis	2 7±0 6	?0±0 8	0 08±0 14	12

8 8 mm² mucus 2 5 mm² vacuoles, 2 4 mm² red granules on fibrils and 0 07 mm² red areas with leucocytes

These values argue in favour of an increased amount of mucus and show the number of enzyme containing granules to be remarkably great

Enzyme containing granules on mucous fibrils were otherwise found in small numbers only in rare cases (one normal and two suspicious of infectious conjunctivitis)

In cases of meibomitis and dacryocystitis a predominantly red mucous thread was found with neutrophilic leucocytes indicating concurrent bacterial conjunctivitis

In papillomatous and follicular conjunctivitis, the mucous thread was seen to be predominantly green and poor in cells as in normal eyes

In the only case of conjunctival phemphigus the rudimentary mucous thread constituted no more than 0 12 mm² mucus and 0 12 mm vacuoles No leucocytes were present

Discussion

In a previous study I showed that iodonitrotetrazolium can be used alone as a vital stain and that this substance allows us to distinguish with fairly great certainty between a sterile and a bacterially infected conjunctiva In normal eyes scattered red granules are seen on a non stained mucous thread In infectious conjunctivitis we find a large diffusely red mucous thread or big red lumps of mucus in the fornix (Norn 1971)

The vital stain mixture described above permits us to distinguish with even greater certainty between sterile and infected conjunctivae because in the slit lamp the amount of red stained matter is directly comparable with that of green mucus

Presence of large red areas means accumulation of neutrophilic leucocytes Smaller red areas may represent accumulations of detritus or rarely enzyme containing granules

Fair agreement has been noticed between the clinical estimate, the colour of the mucous thread as assessed in the slit lamp and the result of microscopy

If in doubt with regard to the diagnosis it can be decided with reasonable certainty whether a conjunctiva is sterile or bacterially infected If the condition is difficult to assess in the slit lamp the diagnosis can be established with greater certainty by microscoping the vital stained mucous thread

I have previously subjected the mucous thread to a quantitative study in the

microscope after vital staining with 1 % alcian blue (Norn 1963) The results refer to the total mucous thread including regions with neutrophilic leucocytes In the present study on the other hand a distinction has been made between the different constituents of the mucous thread

The present investigation gave results bearing out those previously achieved Thus for instance the total mucous thread was demonstrated to have increased in size in infectious conjunctivitis and keratoconjunctivitis sicca Further it was shown that in infectious conjunctivitis the enlargement was due to myriads of neutrophilic leucocytes while in keratoconjunctivitis sicca it was due to an increased amount of mucus and to enzyme containing granules

Conclusion

The tetrazolium alcian blue mixture is *indicated* for vital staining in cases of conjunctival complaints *because* it affords the possibility to determine whether the conjunctiva is sterile or bacterially infected and consequently to decide whether local antibiotic treatment is indicated or not

The above vital stain is further indicated *because* it contributes towards bearing out a diagnosis of chronic simple conjunctivitis This eye disease is characterized by punctate red staining of the superior or the inferior tarsal conjunctiva (Norn 19?c)

Vital staining with a tetrazolium alcian blue mixture is *contraindicated* in the presence of diseases with epithelium bared connective tissue because alcian blue may cause permanent discoloration of the connective tissue (deep keratitis slaked lime corrosion) (Norn 1972b)

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SCANNING ELECTRON MICROSCOPIC STUDIES OF THE TRABECULAR MESHWORK AND THE CANAL OF SCHLEMM – AN ATTEMPT TO LOCALIZE THE MAIN RESISTANCE TO OUTFLOW OF AQUEOUS HUMOR IN MAN

BY

ANDERS BILL and BJÖRN SVEDBERGH

Chamber angle tissue from human eyes was investigated with scanning electron microscopy. The uveal and corneoscleral parts of the trabecular meshwork are described. The endothelial cells of the inner wall of Schlemm's canal are long and slender and at most places are oriented along the lumen of the canal. The average projected surface of a cell towards the canal is about 480 μm². The total number of endothelial cells in the inner wall of the canal is about 23 000. The cells have pores with diameters up to 3(5) μm. The total number of pores is about 20 000. Calculations show that if all the observed pores exist *in vivo* the resistance to outflow in the paths through the endothelial cells is a small fraction of the total resistance to outflow.

Key words: scanning electron microscopy – outflow resistance – aqueous humor – Schlemm's canal – trabecular meshwork.

In adult humans most of the aqueous humor is drained from the anterior chamber into the canal of Schlemm and from there into intra- and episcleral veins; uveoscleral drainage probably plays only a minor role (Bill & Phillips 1971). About 75 % of the total resistance to outflow seems to be located in the

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SCANNING ELECTRON MICROSCOPIC STUDIES OF THE TRABECULAR MESHWORK AND THE CANAL OF SCHLEMM – AN ATTEMPT TO LOCALIZE THE MAIN RESISTANCE TO OUTFLOW OF AQUEOUS HUMOR IN MAN

BY

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Chamber angle tissue from human eyes was investigated with scanning electron microscopy The uveal and corneoscleral parts of the trabecular meshwork are described The endothelial cells of the inner wall of Schlemm s canal are long and slender and at most places are oriented along the lumen of the canal The average projected surface of a cell towards the canal is about 480 μm The total number of endothelial cells in the inner wall of the canal is about 23 000 The cells have pores with diameters up to 3(5) μm The total number of pores is about 20 000 Calculations show that if all the observed pores exist *in vivo* the resistance to outflow in the paths through the endothelial cells is a small fraction of the total resistance to outflow

Key words scanning electron microscopy – outflow resistance – aqueous humor – Schlemm s canal – trabecular meshwork

In adult humans most of the aqueous humor is drained from the anterior chamber into the canal of Schlemm and from there into intra and episcleral veins uveoscleral drainage probably plays only a minor role (Bill & Phillips 1971) About 75 % of the total resistance to outflow seems to be located in the

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chamber angle tissue between the anterior chamber and the canal of Schlemm (Grant 1958) The roles played by each of different layers in this tissue are not clear The routes from the anterior chamber through the uveal portion of the trabecular meshwork seem fairly wide and it has been suspected therefore that most of the resistance is located in the corneoscleral portion of the trabecular meshwork or in the endothelial meshwork close to the canal of Schlemm or in the endothelium of the inner wall of the canal

In monkeys when small particles are perfused through the anterior chamber they tend to be retarded in the endothelial meshwork (Inomata Bill & Smelser 1972) This suggests that the resistance to flow through this region may be high Due to the irregularity of the paths through this meshwork it is not possible however to calculate the resistance to flow

In 1958 Garron Feeney Hogan and McEwen reported that the endothelial cells which constitute the inner wall of Schlemm s canal have large vacuole like spaces Holmberg (1959 and 1965) studied serial sections of these vacuoles with transmission electron microscopy TEM and reported that they have openings both towards the trabecular side and towards the canal of Schlemm The existence of openings from the vacuoles" into the canal was long disputed but recent studies have shown that a fraction of them in fact communicate both with the intertrabecular spaces and the canal of Schlemm (Yamashita & Rosen 1965 Kayes 1967 Tripathi 1968 1971 Inomata Bill & Smelser 1972) The vacuoles" as studied in monkeys appear to be invaginations from the trabecular side into the cells some having more than one opening towards the trabecular side The pores are found at places where an invagination makes the wall very thin The formation of a large invagination does not seem to be a prerequisite for the formation of a pore however since pores are present also in other very thin parts of the cells (Inomata Bill & Smelser 1972) The pores into the canal of Schlemm are so few and so small that a large number of serial sections would be required to evaluate with TEM whether the paths through the invaginations and the pores may account for the flow of aqueous humor into the canal of Schlemm and if so whether they constitute a major part of the total resistance to outflow Recent studies have shown that scanning electron microscopy SEM can be used to study the pores (Bill 1970 Hoffmann & Dumitrescu 1971) The purpose of the present communication is to describe the inner and outer walls of Schlemm s canal in humans and to try to evaluate the flow resistance of the paths through the invaginations and the pores Some observations on the trabecular meshwork will also be described

The results reported in this paper were presented in Uppsala at the twelfth meeting of the Association for Eye Research June 1971 (Svedbergh & Bill 1971)

Material and Methods

Four eyes enucleated because of tumours and seven eyes removed at different times post mortem were studied The four eyes E_C E_M F_R and E were from patients aged 55 56 67 and 55 years respectively with no objective patho logical signs in the anterior segment The intraocular pressures (Schiotz) were 18.5 9 11 and 18 5 mmHg respectively In 3 cases the tumours were malignant melanomas of the posterior segment of the eye and in one case E_C it was a maxillary cancer that had been irradiated In the four tumour cases the anterior chamber was cannulated with two cannulae immediately after the enucleation The chamber was then slowly perfused from one syringe into the outflow cannula care being taken not to raise the eye pressure to high levels The perfused fluid was cold 4 % glutaraldehyde in a 0 05 M sodium phosphate buffer pH 7 4 or 2 5 % glutaraldehyde in mock aqueous humor pH 7 4 (see Bill 1970) The eye was then divided and fixation continued in ice cold glu taraldehyde for at least 60 min. Most preparations were then washed in mock aqueous humor and postfixed for 1 hour in 1 % osmium tetroxide in 0 05 M sodium phosphate buffer pH 7 4 The cadaverous eyes were fixed by perfusion with glutaraldehyde 3–8 hours post mortem and enucleated 0–48 hours later

After fixation the preparations were washed with distilled water and de hydrated for 30 min at each of the following graded ethanol concentrations 30 60 95 and 100 % Some preparations were then airdried Other prepara tions were equilibrated for 30 min in the following ethanol diethyl ether mixtures 30 60 90 and 100 % ether after which they were air dried Still other preparations were equilibrated for 30 min in the following ethanol amyl acetate mixtures (Boyde & Wood 1969) 30 60 90 and 100 % amyl acetate after which they were frozen in liquid nitrogen chilled isopentane and freeze dried

The iris and the ciliary body were usually removed after the preparations had been dried and the chamber angle tissue was then divided into 2–5 *mm* long pieces Two parallel razor cuts were made from the anterior chamber side into the canal near its anterior and posterior ends The chamber angle tissue was then removed and placed on adhesive tape with the inner wall of Schlemm s canal upwards Preparations with the outer wall of Schlemm s canal and preparations with intact trabecular meshwork or torn meshwork were also placed on tape that was glued onto standard stubs These were mounted at an angle of 45 to an evaporation source and rotated while the preparations were coated with a 200–300 Å thick layer of gold or gold palladium in vacuum A Stereoscan (Cambridge Instrument Company England) and a JSM U3

(Japan Electron Optics Laboratory Tokyo Japan) scanning electron microscope were used The accelerating voltage was 5–20 KV

Results

Only the eyes which were perfused with glutaraldehyde immediately after the circulation in the eye had ceased proved suitable for observations of the fine structure of the inner wall of Schlemm s canal Preparations from these eyes were not appreciably influenced by differences in the fixation and drying procedures used In eyes with glutaraldehyde fixation 3–8 hrs post mortem and enucleation 0–48 hrs later the inner wall of Schlemm s canal appeared partly covered by some substance and visible endothelial surfaces appeared rough compared to those observed in freshly fixed eyes It was possible however to determine the size of the endothelial cells also in 2 preparations with late fixation E_K and E_L

The exposure of the inner wall of Schlemm's canal was complicated by the presence of tissue strands between the inner and outer walls of the canal These tissue strands usually made parts of the inner wall remain attached to the outer wall

The trabecular meshwork

The appearance of the chamber angle tissue in a preparation with intact trabecular meshwork is shown in Fig 1 The uveal portion of the meshwork consists of several parts Occasional bands from the periphery of the iris iris processes merge with trabecular cords originating from the iris root These cords branch and unite with each other and with trabecular beams which are continuous with the inner bundless of the longitudinal part of the ciliary muscle At many places where cords unite they form thin sheets The result is an irregular netlike structure with meshes in 1 to 3 inter connecting layers extending from the iris root to the cornea The anterior part is attenuated The openings in the innermost part of the net are large often more than 20 μm those in subsequent layers are smaller Openings in successive layers are only occasionally in register (Fig 2 A) Many openings are bridged over by fine fibrils Small structures which may be cilia were seen in many places

The outer bundles of the longitudinal part of the ciliary muscle are inserted in parts of the scleral spur which appear to break up into corneo scleral sheet Fig 2 B shows corneoscleral meshwork The ciliary muscle with the attached

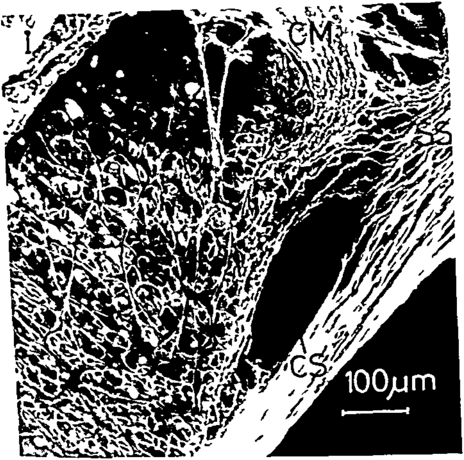
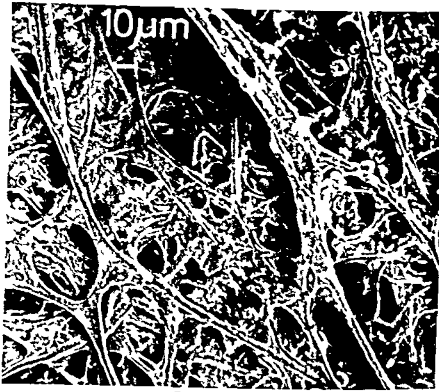


Fig 1

A meridi nal section of the chamber angle tissue The ciliary muscle CM became detached from the sclera during the preparation Uveal cords originatin at the iris root merge with some trabecular sheets which are continuous with lonритudinal bundles f the c liary muscle The outer longitudinal bundles of the muscle merge with trabecu lar sheets orig nating at the scleral spur SS CS is the canal of Schlemm I is iris The preparation was air dried from ethanol

uveal meshwork had been torn from the preparation before the drying Th corneoscleral meshwork consists of several interconnecting sheets the number of sheets decreasing towards the cornea Most of the openings in the exposed sheet are oval with diameters of 10 to 15 μm or less The long axis as a rule is parallel with the circumferential fibres in the trabecular meshwork Over



Figs 2A and B

Detail of preparation shown in Fig 1 Uveal portion of the trabecular meshwork with partly overlapping openings B Detail of corneoscleral meshwork The ciliary muscle with the attached meshwork had been stripped from the preparation to give a clear view of the first corneoscleral sheet extending from the scleral spur to the cornea. U are remains of uveal meshwork The openings seen in the trabecular sheet are oval with diameters around 15 µm The preparation was air dried from ethanol

lapping of the openings in different sheets is unusual The borders and the nuclei of the endothelial cells that cover the meshwork cannot be seen clearly

The inner wall of Schlemm s canal

Fig 3 A and B show relatively large parts of the inner wall of Schlemm s canal with remains of broken tissue strands Structures about 10 µm long and 3–5 µm wide bulge into the lumen of the canal most of them with the longitudinal axes oriented parallel to the canal The number of bulging structures varies greatly from one area to another On the inner wall can be seen places where the wall is split into two layers the superficial being in the form of a small perforated septum With high magnification structures most probably repre



b

senting cell borders can be seen (Fig 4) These structures indicate that many cells are more than 100 µm long and about 4–8 µm wide At most places the cells are oriented along the lumen of the canal It was assumed that all nuclei of the endothelial cells bulge into the lumen and that every bulging structure represented a nucleus The surface of each cell facing the canal of Schlemm could then be calculated Such calculations were made on material from 6 eyes (Table I) The mean value was 482 μm^2 The area investigated in each eye was at least 158 000 µm The surface of the inner wall of Schlemm s canal has many ridges The actual canal surface of each endothelial cell is thus considerably larger than the value for the projected area given above

Part of the bulging structure mentioned above has no folds and is assumed to contain the nucleus of the cell Another part of the bulging structure has folds and appears partly collapsed especially in air dried preparations This part supposedly represents one or several invaginations from the trabecular side Previous results obtained in monkeys support these assumptions (Bill 19 0) Invaginations that are not partly supported by a nucleus tend to collapse completely Some of the invaginations have small openings into the canal of Schlemm (Fig 5 6) and such pores can be seen also at places where there

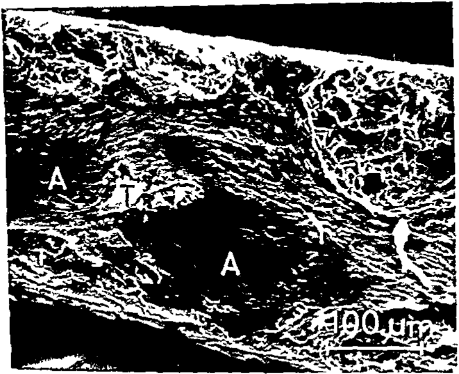


a

Figs 3A and B

The inner wall of the canal of Schlemm Several tissue strands T were broken when the canal was opened and large parts of the inner wall were lost S is a perforated septum appearing on the inner wall About 10 µm long structures bulge into the lumen of the canal These are nuclei and associated vacuoles At most places the bulging structures suggest a preferential flow direction At the tissue strands there are large areas A with very few bulging structures These areas appear to be places with little flow of aqueous humor Freeze dried preparation

is no apparent invagination Two or more pores are sometimes found close to each other and seem to open into the same invagination The number of openings and the diameters of the openings were determined in large areas in the four eyes that had been subjected to rapid fixation Only circular or oval openings with rounded edges were regarded as pores The areas investigated were chosen at random but areas with obvious artifacts such as long breaks were discarded The areas close to the incisions as a rule were not suitable for pore counting The total area investigated was 42 400 µm in the eye E_M and 75 000 µm² in each of the other eyes Table I shows the results The mean pore frequency was 1840 pores/mm projected area of the inner wall Fig 7 shows

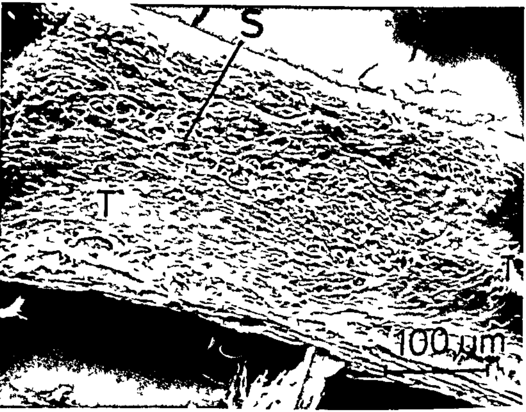


b

the frequency distribution of the pore sizes in the four eyes The pore sizes were measured on the fluorescent screen of the microscope and estimated to the nearest 0 1 µm Because of the paucity of pores in each size group the pores were then classified into groups with bigger limits

The outer wall of Schlemm s canal

Structures representing cell borders could be seen clearly in many places The cells are long and slender The cell nuclei bulge somewhat into the lumen of the canal Most cells are parallel to the canal but at the entrance of a col lector channel this pattern is sometimes broken (Fig 8) Septa crossing the entrances of the collector channels are seen at many places (Fig 9) Most entrances are oval with maximum diameters of 20– 0 µm Structures which might be collapsed vacuoles were not seen in the outer wall and there were no pores of the type found in the inner wall of the canal

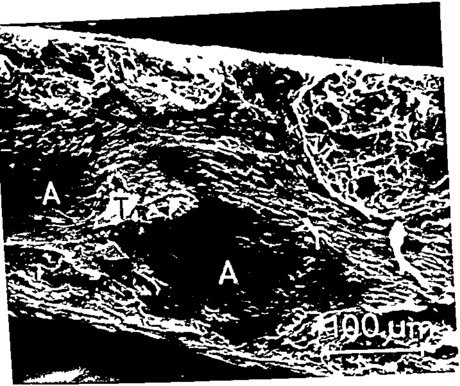


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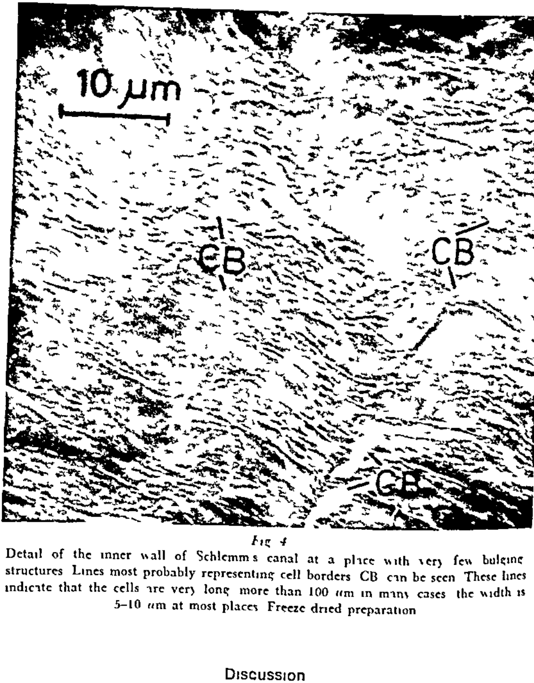


Fig. 4
Detail of the inner wall of Schlemm's canal at a place with very few bulging structures. Lines most probably representing cell borders (CB) can be seen. These lines indicate that the cells are very long, more than 100 µm in many cases; the width is 5–10 µm at most places. Freeze dried preparation.

Discussion

The trabecular meshwork

Ashton, Brini & Smith (1956) have given detailed descriptions of the trabecular meshwork as seen with light microscopy. Spencer, Alvarado & Hayes (1968), Hansson & Jerndal (1971) and Anderson (1971) have described the general appearance of the meshwork as seen with SEM and Hogan, Alvarado & Weddell (1971) have summarized previous and new studies with TEM. The

Table I
Projected surface per cell and number of pores per mm projected surface of the inner wall of Schlemm's canal

Eye	Projected surface per cell in μm	Pores per mm projected surface
E_C	358	2130
E_M	405	2100
E	429	1775
E_P	6[illegible]	1350
E_K	478	not invest
E_L	571	not invest
Mean value	482	1840

results of our study agree with the concept of a uveal and corneoscleral portion of the trabecular meshwork both portions extending to the cornea The trabecular sheets which are continuous with the ciliary muscle merge both with uveal cords originating at the iris root and with corneoscleral sheets originating at the scleral spur The sheets from the muscle have been classified as belonging both to the corneoscleral meshwork (see Hogan Alvarado & Weddell 1971) and also to the uveal meshwork (see Ashton Brini & Smith 1956 and Fine 1964) Since the muscle is part of the uvea the latter assignment would seem logical

Vegge (1963) has described cilia on the trabecular beams in man This makes it seem likely that the cilia like structures that we found scattered in an irregular way on the trabecular cords and sheets are in fact cilia

SEM is helpful in giving a good view of the general arrangement of the trabecular meshwork but adds little new information about this structure

The canal of Schlemm

It has been pointed out by Holmberg (1965) that the ultrastructure of the chamber angle tissue in man is very similar to that in monkeys This is true also for the surface structures seen by SEM There are some differences that should be pointed out however As noted also by Holmberg (1965) there are fewer septa and tissue strands in the canal of Schlemm in humans The cells of the inner wall of Schlemm's canal are larger in humans than in monkeys



Fig 5

Detail of the inner wall of Schlemm s canal A partly collapsed bulging structure has two openings P1 and P2 Part of the nucleus N can be seen through one opening Structures most probably representing collapsed invaginations Cl are seen at several places P3 is also a pore Freeze dried preparation

SEM suggests that the average projected cell surface facing the lumen is 482 µm in man and 253 µm in monkeys (Bill 1970) Lutjen Drecoll & Rohen (1970) using a silver impregnation technique found average values of 408 μm^2 in man and 252 µm in vervet monkeys In man the projected surface of the inner wall of Schlemm s canal is 11 mm (see McEwen 1958) The total number of cells of the inner wall is thus about 23 000

The results of the present study suggest that the flow of aqueous humor

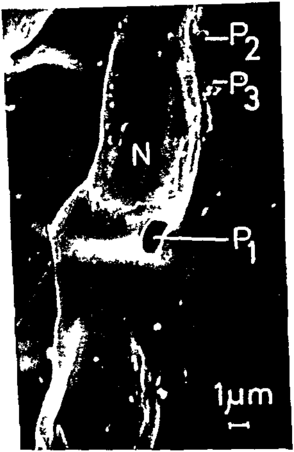


Fig 6
Cell with the nucleus N bulging into the lumen of Schlemm s canal has a partially collapsed invag nation with a pore P1 Two small pores P? and P3 can also be seen Freeze dried preparation

within the canal of Schlemm has an influence on the orientation of the endo thelial cells This influence is seen both on the inner and outer walls (Fig 3 A and B Fig 8) at most places the bulging nuclei and cell borders suggest a pref erential flow direction

Rohen (1969) has described two kinds of collector channels which drain fluid from the canal of Schlemm one had diameters around 70 µm the other had diameters around 35–50 µm The distance between the openings into the canal of Schlemm of the collector channels was reported to be 0 4–2 7 mm In the

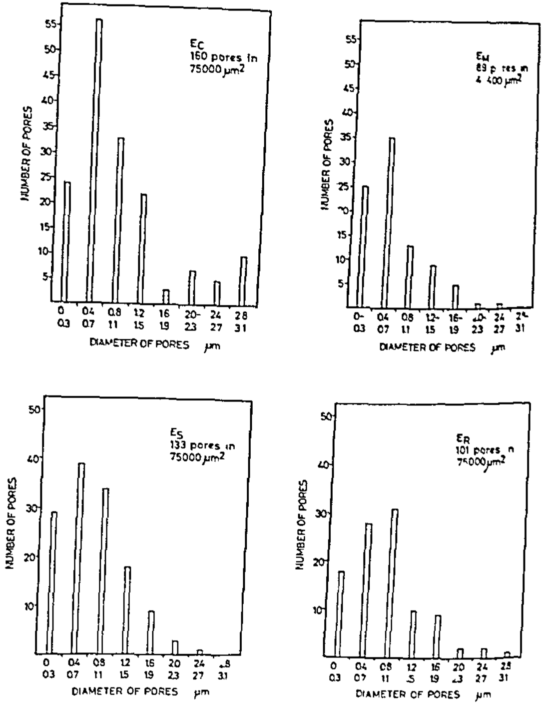


Fig.

The pores in large areas of the inner wall of Schlemm's canal were investigated in 4 eyes E_C, E_M, E_S and E_R. The diagrams show the distribution of the pore sizes. The number of pores counted and the areas investigated are given in the diagrams. Two pores not shown in the diagram for E_C had diameters of 4.5 and 5 μm.



Fig 8
Part of the outer wall of Schlemm s canal w th an opening into a collector channel CC The nuclei of the endothelial cells N bulge into the lumen of the canal The cells seem to be oriented along preferential flow directions Air dried preparation.

present study openings were found into both wide and narrow collectors and the distance between the openings also agrees with that in the eyes observed by Rohen

The septa and tissue strands in the canal of Schlemm which may help to keep the canal open (Bill 1970 Hoffman & Dumitrescu 1971) probably make it impossible to remove a part of the outer wall without tearing the inner wall This may be of importance for the result of the sinusotomy operation described by Krasnov (1968) The aim of the operation is to facilitate the outflow from the canal of Schlemm by removing part of the outer wall of the canal The results of the present study suggest that such an operation also tends to create defects in the inner wall endothelium and the adjacent endothelial meshwork. Such defects may make the operation useful not only in glaucomatous cases



Fig 9
Part of the outer wall of Schlemm s canal with a septum S across the opening into a collector channel N nuclei Freeze dried preparation

with high resistance in the sclera but in cases with high resistance in the endothelial meshwork and the inner wall endothelium as well

Pore sizes and frequencies

It is possible that the processing of samples for SEM especially the drying tends to create pores at places where the endothelial cells are very thin Large discrepancies between results obtained with SEM and TEM therefore would call for a cautious evaluation of data obtained with SEM

The pore frequency found in the present study in the inner wall of Schlemm s canal was about 1800 pores per mm projected inner wall area This figure is not very different from that observed in vervet monkeys which is about 1200 per mm² (Bill 1970) These figures are representative for the middle /₃ of the canal the areas close to the anterior and posterior ends could not be

investigated Segawa (1970) using a replica technique which did not involve drying found about 1000 pores per mm of the inner wall in human eyes Kaves (1967) in a study with TEM reported a pore frequency of about 350–500 pores per mm length of the canal of Schlemm This corresponds to about 1000–1500 pores per mm inner wall Cole & Tripathi (1971) used data obtained with TEM (Tripathi 1968) to calculate the resistance in the paths through the vacuoles It can be seen from their data that the number of openings into the canal of Schlemm was estimated to range from 230 to 2000 The almost tenfold difference illustrates the difficulty in estimating pore frequencies from TEM and the following will show that even the higher figure may be too low In his study in rhesus monkeys Tripathi (1968) found maximum diameters of the endothelial cells of 8–12 μm and exceptional cells measured 20 μm With these dimensions of the cells about 50 % of them had a vacuole" and 2 % of the vacuoles had openings into the canal of Schlemm The inner wall of Schlemm s canal was so wrinkled that the true surface was assumed to be 40 mm (Cole & Tripathi 1971) Tripathi in giving maximum diameters of the cells seems to regard them as approximately oval a reasonable surface area of the cells towards the canal of Schlemm would then be 50 μm This would mean that the number of endothelial cells should be 40 000 000/50 or 800 000 As mentioned above the endothelial cells are long and slender with an average projected surface towards the canal of Schlemm of about 250 μm in monkeys and 480 μm in man The true number of cells is thus much smaller than 800 000 both in monkeys and man but this can be neglected for the moment With 800 000 cells and vacuoles in every second cell the number of vacuoles would be 400 000 Two per cent of the vacuoles had openings into the canal of Schlemm that is about 8000 This value corresponds to a pore frequency of about 700–800 pores/mm^2 projected area of the inner wall a value that is not very different from the values obtained with SEM in vervet monkeys (Bill 1970)

A study with both SEM and TEM in material from the same eye would be of interest in resolving definitely whether the two methods give the same pore frequencies With the pore frequency and the pore size distribution known from the study with SEM it should be possible to calculate approximately the changes of finding pores in sections taken at random from different parts of the canal of Schlemm

The pores found in the present study had diameters up to 3 and exceptionally 5 μm Most studies with TEM in man and monkeys and SEM in monkeys have given values in agreement with Holmbergs report of 0.3–2 μm (1965) It is not surprising that SEM reveals a few large pores which are very unlikely to be found with TEM due to their low frequency



Fig 9
Part of the outer wall of Schlemm s canal with a septum S across the opening into a collector channel N nuclei Freeze dried preparation

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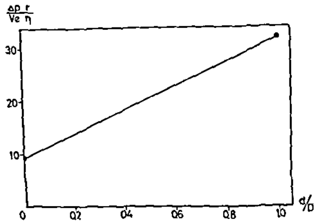


Fig 11

Diagram used to interpolate values of the dimensionless expression used in the calculation of resistance according to method 2 See text page 316

path through a cell and the simplified model used in the calculations that follow It is further assumed that the pore frequency and pore size distribution found in the middle ²/₃ of the canal pertain for the whole inner wall and that the pressure drop across all pore invagination units is the same With these assumptions resistance to flow can be calculated in two ways

Table II

Resistance in different pores and pore invagination units calculated according to method 1 see text.

Pore diameter μm	Apparent pore length μm	Resistance in each pore mmHg min μl⁻¹	Resistance in each pore invagination mmHg min μl⁻¹
0.2	0.3–0.4	338 000	839 000
0.6	0.4–0.7	19 090	19 910
1.0	0.6–0.9	3910	4100
1.4	0.8–1.1	1093	1913
1.8	1.1–1.4	467	1357

THE RESISTANCE TO OUTFLOW OF AQUEOUS HUMOR

McEwen (1958) used Poiseuille's law to calculate the number of pores that would be required to account for the drainage of aqueous humor into the canal of Schlemm He found that if the pore length was 20 μm 1200 pores with a diameter of 2 μm would be required or one pore with a diameter of 12 μm or 110 000 pores with a diameter of 0 6 μm With data available for the actual number of pores and the pore sizes it is now of interest to analyze whether the outflow paths represented by the invaginations and their pores can account for all the drainage of aqueous humor into the canal of Schlemm or just a small fraction As pointed out by McEwen (1958) calculations of the resistance in short narrow and irregular paths require several assumptions It is assumed in the following that all pores seen with SEM contributed to aqueous drainage *in vivo* that they were located in the walls of invaginations and that there was only one pore in each invagination In fact some pores appeared to be located in flat parts of the cells and some pores seemed to belong to the same invaginations It is also assumed that the invagination into an endothelial cell may be represented by a tube 3 μm long and 2 μm wide In fact both invaginations and entrances into invaginations vary in size but the figures given seem reasonable from studies both in man and in monkeys (Holmberg 1965 Inomata Bill & Smelser 1972) The length of the pores in the walls of the invaginations is assumed to be 0 3 μm Fig 10 shows a schematic model of the

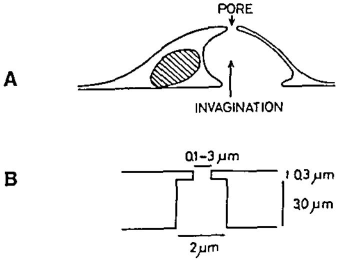


Fig 10

A Invagination and pore in an endothelial cell B Simplified model used to calculate resistance to flow See text

Method 1

It is assumed that the flow through the invagination has no influence on that through the pore and that both the pore and the invagination are too short to permit the use of Poiseuille's law without corrections

According to Poiseuille's law the flow Q through a tube is a function of the pressure drop Δp along the tube the radius r of the tube the length L of the tube and the viscosity η of the fluid

$$Q = \frac{\Delta p}{8} \frac{\pi}{L} \frac{r^4}{\eta} \tag{1}$$

The flow through an aperture that is an opening with a length that is very small compared with the radius (Happel & Brenner 1965) is given by the equation

$$Q = \frac{\Delta p \; r^3}{3\eta} \tag{2}$$

Combining the two equations gives the apparent length of an aperture

$$L = 1.18\ r \tag{3}$$

Therefore it seems reasonable that the flow through a pore with a radius of 0.5 μm and a length of 0.3 μm encounters a resistance that corresponds to an apparent pore length of 0.6–0.9 μm Table II shows calculations of resistances in different pores based on analogous assumptions concerning the apparent length of the other pores To avoid an underestimate of the resistances in the pores the maximum lengths were used The flow through the invagination might also be influenced by the shortness of the path Again to avoid underestimating the resistance it was assumed that the apparent length of the invagination was 4 μm The resistance in each invagination or vacuole that has a pore into the canal would then be 0.89×10^3 mmHg min μl^{-1} Table II shows the resistance in the different pore invagination units and Table III the total resistance in each pore invagination class and also the conductivities Invagination pore units with 0.1 0.2 and 0.3 μm pores were referred to the 0.2 μm class those with diameters of 0.4 0.5 0.6 and 0.[illegible] to the 0.6 μm class etc The resistance in pores with a diameter of 2 μm and more was regarded as negligible compared to that in the invagination The equations (1) and (2) apply only if flow is laminar Calculations of the Reynolds numbers for the different pores showed that the numbers were about 10^{-3} which is far from the critical level of 2000 at which flow becomes turbulent The total resistances in the endothelium in the eyes E_C E_M E_S and E_R were 0.16 0.25 0.21 and 0.24 mmHg min μl^{-1} respectively

Table III

Total resistance and conductivity in pores and invaginations in eyes E_C E_M E_S and E_R calculated according to method I see text

Pore invagination class pore diameter in μm	Number of pore invaginations in one eye				Total resistance in pore invaginations mmHg min μl^{-1}				Total conductivity in pore invaginations μl min^{-1} mmHg^{-1}			
	E_C	E_M	E_S	E_I	E_C	E_M	E_S	E_R	E_C	E_M	E_S	E_R
0 2 (0 1–0 3)	3528	6475	4251	2641	252	137	209	337	0 004	0 007	0 005	0 003
0 6 (0 4–0 7)	8232	9065	5717	4108	2 42	2 20	3 48	4 85	0 413	0 455	0 287	0 206
1 0 (0 8–1 1)	4851	3367	4984	4548	0 85	1 22	0 82	0 90	1 183	0 821	1 216	1 109
1 4 (1 2–1 5)	3234	2331	2639	1467	0 59	0 82	0 72	1 30	1 691	1 219	1 380	0 767
1 8 (1 6–1 9)	441	1295	586	587	3 07	1 05	2 32	2 31	0 325	0 954	0 432	0 433
2 0 (2 0–5 0)	2235	518	1319	1467	0 40	1 72	0 67	0 61	2 511	0 582	1 482	1 648
Total	22 521	23 051	19 496	14 818	0 16	0 25	0 21	0 24	6 127	4 038	4 802	4 166

The radius r in this example is 0.3 μm η = 0 007 poise (viscosity of water at 37°C) With due consideration of the units involved the resistance is then 16 000 mmHg min μl⁻¹ Results obtained with this method are given in Table IV This method results in resistance values of 0 15 0 24 0 21 and 0 24 mmHg min μl⁻¹ in the eyes E_C E_M F_S and E_P respectively

The values for resistance to outflow calculated above are highly approximate but are still of interest They indicate that the paths through the invaginations or vacuoles are quite sufficient to account for the flow of aqueous humor into Schlemm s canal The resistances to outflow in the eyes investigated are not known but usual values in man are about 3–5 mmHg min μl⁻¹ (Grant 1959) Thus the calculated total resistance in the pathways through the endothelium of the inner wall of Schlemm s canal appears to be less than 10 % of the total resistance to outflow Since only about 25 % of the total resistance to out flow is located in the sclera (Grant 1958) and since there are large partly overlapping openings in the innermost part of the trabecular meshwork the main resistance to outflow is likely to be located in the outer part of the trabe cular meshwork and in the endothelial meshwork

It is of interest now to consider the way in which aqueous humor actually passes through the trabecular and endothelial meshwork It can be calculated that if the total resistance to flow from the anterior chamber into the canal of Schlemm was 3 mmHg min μl⁻¹ and if each pore had its own strictly private pathway through the meshwork and each of these pathways through the mesh work had the same resistance this resistance would be about 40 000 mmHg min μl⁻¹ A comparison between this value and the resistance values in Table II indicates that under such conditions the main pressure drop in path

Table IV
Value of dimensionless term and resistance of each pore invagination calculated according to method 9 see text

Pore diameter μm	Value of $\frac{\Delta p \ r}{Ve \ \eta}$	Resistance in each pore invagination mmHg min μl⁻¹
0 2	11 8	329 000
0 6	16.3	16 800
1 0	20 8	4640
1 4	25 3	2130
1 8	29 8	1150
0	37 0	890

Method 2

The other way to calculate the resistance in the pore invagination units is to apply the "limiting case" method used in hydrodynamic engineering (Hutte 1955) Let the diameter of a pore = d and the diameter of an invagination = D One limit occurs when $d/D \rightarrow 0$ that is when the pore diameter is very small We may then neglect the resistance in the preceeding invagination and apply the aperture formula (2) which may be written

$$\frac{\Delta p \quad r}{Ve \quad \eta} = 3 \quad \pi \tag{4}$$

where Ve is the mean linear velocity in the pore The other limit occurs when $d/D \rightarrow 1$ that is when the pore diameter equals the diameter in the invagination We may then neglect the resistance in the pore and apply Poiseuille's law to the invagination

$$\Delta p = \frac{Q \quad 8L \quad \eta}{\pi \quad r^4} \tag{5}$$

On the assumption justified above that the apparent length of the invagination is $L = 4r = 4\ \mu m$

$$\Delta p = \frac{Ve \quad r^2 \quad \pi \quad 8 \quad 4r \quad \eta}{\pi \quad r^4} = \frac{Ve \quad 32 \quad \eta}{r} \tag{6}$$

which gives

$$\frac{\Delta p \quad r}{Ve \quad \eta} = 32 \tag{7}$$

Thus the two extreme values of the dimensionless expression given by equation (4) and (7) are 3π and 32 It is now assumed that intermediate values of d/D give intermediate values of the dimensionless expression and that linear interpolation can be used (Fig 11) Such an interpolated value of the dimensionless expression can then be used to estimate the resistance in the pore invagination unit As an example for a unit with a pore diameter of 0 6 μm the ratio d/D is 0 3 and the value of the dimensionless expression interpolated from the diagram in Fig 11 (page 313) is 16 3

$$\frac{\Delta p \quad r}{Ve \quad \eta} = 16\ 3$$

The resistance R is equal to $\Delta p/Q$ and $Q = Ve \quad \pi \quad r$

$$\text{Thus } R = \frac{\Delta p}{Q} = \frac{16\ 3 \quad \eta}{\pi \quad r^3}$$

The radius r in this example is 0 3 μm η = 0 007 poise (viscocity of water at 37°C) With due consideration of the units involved the resistance is then 16 000 mmHg min μl 1 Results obtained with this method are given in Table IV This method results in resistance values of 0 15 0 24 0 21 and 0 24 mmHg min μl 1 in the eyes E_C E_M E_S and E_R respectively

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It is of interest now to consider the way in which aqueous humor actually passes through the trabecular and endothelial meshwork It can be calculated that if the total resistance to flow from the anterior chamber into the canal of Schlemm was 3 mmHg min μl 1 and if each pore had its own *strictly private* pathway through the meshwork and each of these pathways through the mesh work had the same resistance this resistance would be about 40 000 mmHg min μl 1 A comparison between this value and the resistance values in Table II indicates that under such conditions the main pressure drop in path

Table IV

Value of dimensionless term and resistance of each pore invagination calculated according to method 2 see text

Pore diameter μm	Value of $\frac{\Delta p \quad r}{Ve \quad \eta}$	Resistance in each pore invagination mmHg min μl 1
0	11 8	3[illegible]9 000
0 6	16 3	16 800
1 0	20 8	4640
1 4	25.3	2130
1 8	[illegible]9 8	1130
[illegible] 0	3[illegible] 0	890

ways ending with 0 2 μm pores would be located in the inner wall endothelium but in all pathways ending with 0 6 μm or larger pores the main pressure drop would occur in the trabecular meshwork However the structure of the endothelial meshwork and that of the outer part of the meshwork as seen with TEM indicate that there are many sideways communications in these regions These communications will make the large pores drain larger regions of meshwork than small pores As a consequence the pressure drop across the endothelium of the inner wall of Schlemm s canal will be more even than discussed above If there were negligible resistance to flow in the sideways paths as was assumed in the calculations of resistances the pressure drop across the endothelium would be uniform and less than 10 % of the total pressure drop between the anterior chamber and the episcleral veins

In the case of very poor sideways communications in the meshwork close to the canal of Schlemm one can expect the formation of new pores or enlargement of the smallest pores to reduce the resistance to outflow Such a reduction will be marked if the new or enlarged pores drain regions of the trabecular meshwork which previously contained stagnant fluid Thus if 10 000 new pores with a diameter of 2 μm are produced by a drug 10 000 pathways through the trabecular meshwork will become activated each having a resistance around 40 000 mmHg min μl^{-1} The total resistance between the anterior chamber and the canal of Schlemm about 3 mmHg min μl^{-1}, will then be reduced to 1 7 mmHg min μl^{-1} In the case of good communications within the meshwork close to the canal the same number of new pores would have a small effect on the total resistance due to the fact that they make a small part of the total resistance – about 10 % – even smaller

Flow through so called Sondermann channels (Sondermann 1933) and flow between the endothelial cells (Rohen & van der Zypen 1968) and pinocytosis (Fine 1964 Feeney & Wissig 1966) have been suggested as accounting for or contributing to the drainage of aqueous humor into the canal of Schlemm (see also Hogan Alvarado & Weddell 1971 and Cole & Tripathi 1971) The results of the present investigation of course do not exclude the existence of such alternative pathways but they indicate that under normal conditions there is no need for such routes

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SCANNING ELECTRON MICROSCOPIC STUDIES OF THE CORNEAL ENDOTHELIUM IN MAN AND MONKEYS

BY

BJÖRN SVEDBERGH and ANDERS BILL

The inside of the cornea from human and monkey eyes was investigated with scanning electron microscopy In man four zones can be distinguished Zon I includes most of the cornea The cells are usually hexagonal occasionally pentagonal The cells overlap to a great extent and the nuclei cause low flat bulges Few cells have cilia Drop like structures and pits are scattered over the cell surface and probably represent micro villi and openings into pinocytotic vesicles respectively The cell borders show much interdigitation and occasional cells have stick like structures bridg ng over the border Zone II is 500–1000 μm wide There is less overlapping of the cells and about 50 % have a 2–7 μm long central cilium A few cells have 2–4 cilia The nuclei bulge less than in Zone I Zone III is about 50–150 μm wide In adult human eyes it has an ir regular surface due to the presence of Hassall Henle s warts Some cells h ve cilia. Zone IV lies between Zone III and the trabecular meshwork It is about 50–100 m wide and has no warts The endothelial cells are less regular than in the other zones Cilia are less frequent than in Zone II Isolated trabecular cords and openings into subendothelial extensions of the trabecular meshwork are seen In monkeys the cells of Zone I have

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no cilia and the cilia of Zone II are scarce No or few Hassall Henles warts were seen and there was no other feature to distinguish Zone III from Zone IV

Key words scanning electron microscopy – cornea – endothelium –cilium – cell border – Hassall Henles warts

The corneal endothelium is a monolayer of mostly hexagonal cells of mesodermal origin facing posteriorly the anterior chamber and anteriorly its basement membrane Descemets membrane The structure of the posterior surface has been reconstructed from extensive light and transmission electron microscopic (TEM) studies (see Donn 1966 Ehlers 1966) Recently direct methods of studying the surface structure have been applied A replica technique was used by Wolf (1968 1969) and studies with scanning electron microscopy (SEM) in rabbits were reported by Blümcke & Morgenroth (1967) Studies on human eye with SEM (Spencer et al 1968 Tripathi 1969 Hager Hoffmann & Dumitrescu 1971 Hansson & Jerndal 1971) were centred on the trabecular meshwork and gave little new information about the surface ultrastructure of the corneal endothelium

The purpose of the present communication is to report some observations made with SEM on the surface ultrastructure of the cornea in humans and monkeys A preliminary report was given in Uppsala at the twelfth meeting of the Association for Eye Research June 1971 (Svedbergh & Bill 1971)

Material and Methods

The human material consisted of 14 eyes Seven eyes enucleated because of tumours were fixed immediately after surgery The other seven eyes were fixed 3–8 hrs post mortem Three of the eyes with tumours were fixed after division The other eleven were identical with those subjected to an earlier study of Schlemms canal and trabecular meshwork (Bill & Svedbergh 1972) These eyes were fixed by perfusion of the anterior chamber In no case were there any objective signs or anamnesis of glaucoma or pathological involvements of the anterior segment of the eye The ages of the patients ranged from 13 to 88 years

The monkey species investigated were Macaca mulatta (3 eyes) Macaca irus (4 eyes) Macaca speciosa (2 eyes) and Cercopithecus ethiops (4 eyes) There

were no objective signs of eye disease Fixation was accomplished by perfusion of the anterior chamber (Bill 1970) The first fixative was glutaraldehyde and the further processing consisted in short of dissection in glutaraldehyde post fixation in osmium tetroxide followed by different dehydration procedures (air drying from ether or alcohol or freeze drying from amyl acetate) The tissue specimens were placed on adhesive tape glued on standard stubs and coated with gold or gold/palladium by evaporation in vacuum A Stereoscan (Cambridge Instrument Company England) and a JSM U3 (Japan Electron Optics Laboratory Tokyo Japan) scanning electron microscope were used For details of methods see Bill & Svedbergh (1972)

Results

Only those eyes which were perfused immediately after circulation in the eye had ceased proved suitable for observation of the fine structural details of the posterior surface of the corneal endothelium Preparations from these eyes were generally similar irrespective of the fixation and drying procedures used In eyes which were fixed 3–8 hrs post mortem the surface seemed rough and often littered while fine details such as cilia were distorted if observable at all

HUMAN CORNEA

The endothelial cells covering the posterior surface of the cornea are mostly hexagonal occasional cells are pentagonal Most cells have a diameter around 20–25 μm but diameters ranging from 10 to 45 μm are seen especially in eyes of elderly patients With an average diameter of 20 μm the cell surface *of each cell towards* the anterior chamber is approximately 250 μm^2 The total surface of the cornea covered by endothelial cells is about 100 mm Each cornea thus has roughly about 400 000 endothelial cells

The posterior surface of the adult human cornea can be divided conveniently into four parts Zones I–IV each having certain characteristics of surface structure as detailed below (Fig 1) Zone I includes the central and intermediate part of the cornea Next lies zone II 500–1000 μm wide Zone III is about 50–150 μm wide and Zone IV 50–100 μm wide lies immediately adjacent to the trabecular meshwork

no cilia and the cilia of Zone II are scarce. No or few Hassall-Henle's warts were seen and there was no other feature to distinguish Zone III from Zone IV.

Key words: scanning electron microscopy – cornea – endothelium – cilium – cell border – Hassall-Henle's warts.

The corneal endothelium is a monolayer of mostly hexagonal cells of mesodermal origin, facing posteriorly the anterior chamber and anteriorly its basement membrane, Descemet's membrane. The structure of the posterior surface has been reconstructed from extensive light and transmission electron microscopic (TEM) studies (see Donn 1966, Ehlers 1966). Recently, direct methods of studying the surface structure have been applied. A replica technique was used by Wolf (1968, 1969) and studies with scanning electron microscopy (SEM) in rabbits were reported by Blümcke & Morgenroth (1967). Studies on human eye with SEM (Spencer et al. 1968, Tripathi 1969, Hager, Hoffmann & Dumitrescu 1971, Hansson & Jerndal 1971) were centred on the trabecular meshwork and gave little new information about the surface ultrastructure of the corneal endothelium.

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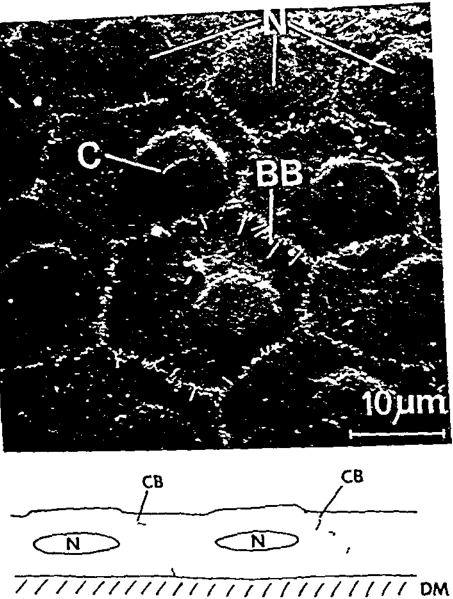


Fig 2

Detail from the central cornea Zone I The endothelial cells are hexagonal occasionally pentagonal The nuclei N are represented by low flat bulges The cells overlap to a great extent so that visible cell borders may run near or across the nuclei Borders bars BB and a cilium C, can be observed The type of overlapping is shown in the insert DM is Descemet's membrane CB is cell border The preparation was freeze-dried

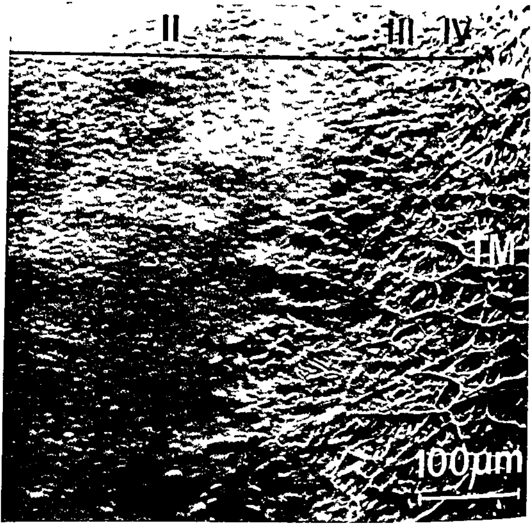


Fig 1
The peripheral part of the inside of the cornea and the trabecular meshwork TM Corneal zones are indicated by their number Zone II is characterized by its ciliated cells Zone III by Hassall Henle s warts and Zone IV by the subendothelial circum ferential strands The preparation was air dried from ether

Zone I

The most striking feature of this zone is the low flat bulges caused by the round or slightly oval 5–10 µm long cell nuclei (Fig 2) Towards the periphery the bulges are less distinct The cells generally overlap to a great extent so that cell borders often pass across the bulges caused by the nuclei Mitotic cells are very rare The cell borders have as a rule a zigzag appearance due to interdigitations (Fig 3) Some of the interdigitating processes are not properly anchored to the underlying cell surface and thus have a free end floating in



Fig 4
Detail from Zone II About 50% of the endothelial cells have a centrally located cilium C The preparation was freeze dried

0 1–0 2 μm are seen scattered over the cell surface They number approximately 10–40 per cell Pits with a diameter of about 0 1 μm are also observed scattered over the cell surface Cilia are sparse They are centrally located and of smaller size than in Zone II and III (see below)

Zone II

In this zone the cell nuclei are less prominent and more centrally located in the

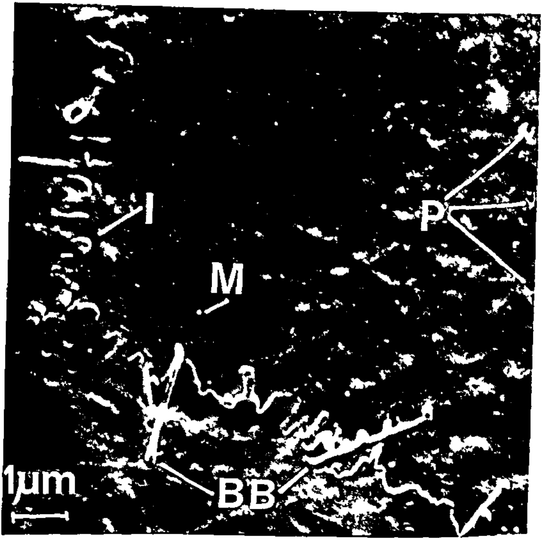


Fig 5
Detail of the cell border Interdigitations I give the border a zig zag appearance Border bars BB bridge over the border mostly at right angles Small pits P are seen scattered over the cell surface. They probably represent openings into pinocytotic vesicles M drop like structures which probably represent microvilli The preparation was freeze dried

the aqueous humor Stick like structures in the following called border bars are occasionally seen bridging over the cell border These structures are fre quent around some cells and absent around others The border bars are about 3–6 µm long and less than 1 µm wide and usually lie at right angles to the border line

Drop like structures occasionally elongated and curved with a diameter of



Fig 4
Detail from Zone II About 50 % of the endothelial cells have a centrally located cilium C. The preparation was freeze dried

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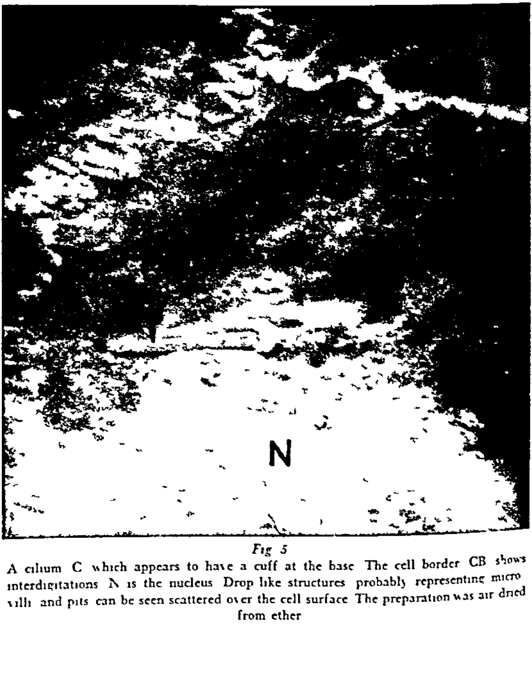


Fig 5

A cilium C which appears to have a cuff at the base The cell border CB shows interdigitations N is the nucleus Drop like structures probably representing micro villi and pits can be seen scattered over the cell surface The preparation was air dried from ether

cell There is thus a smaller degree of overlapping of the cells (Fig 4) The cell borders and surface have essentially the same appearance as in Zone I

A centrally located cilium can be seen in approximately 50% of the endothelial cells The cilium is 2–7 μm long and often appears to have a cuff at the base (Fig 5) A few cells have 2–4 cilia (Fig 6) Many cilia have a club like end



Fig 6

An endothelial cell with 3 cilia The cilia have a club like end The cell border CB shows interdigitations and border bars BB There are many drop like structures and pits Openings with halos at the border are electron beam artifacts A seen when high accelerating voltage was used The preparation was air dried from ether

Zone III

In most adult human eyes this zone resembles a cobblestone pavement This is due to the presence of Hassall Henle s warts Fig 7 These warts are dome shaped excrescences of Descemet s membrane covered by endothelial cells We have verified their nature by light microscopy The warts have diameters of 30–80 μm Warts were occasionally observed in other parts of the cornea too

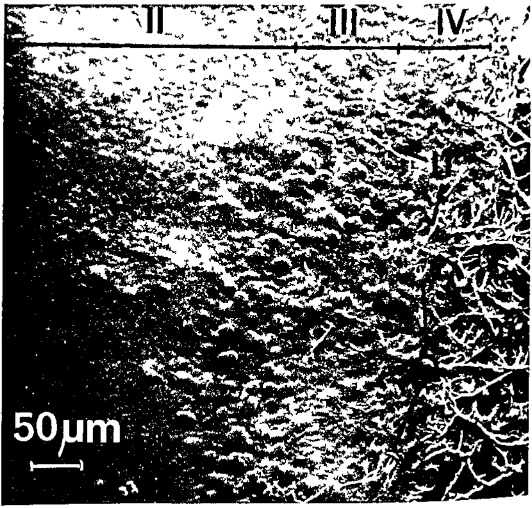


Fig 7

Survey of the peripheral corneal endothelium with Zones II–IV TM is the trabecular meshwork Hassall Henle s warts give Zone III a cobblestone appearance but are also seen in Zone II a condition known as cornea guttata Isolated trabecular cords IT and openings O through which the subendothelial extension of the trabecular mesh work can be seen are observed in Zone III and IV The preparations was air dried from ether

The nuclei of the cells covering the warts seemed to have a tendency to ac cumulate at the base of the warts (Fig 8)

Zone IV

Between the region with warts and the trabecular meshwork proper is a 50–100 µm wide rather flat area where the endothelial corneal cells are irregular in

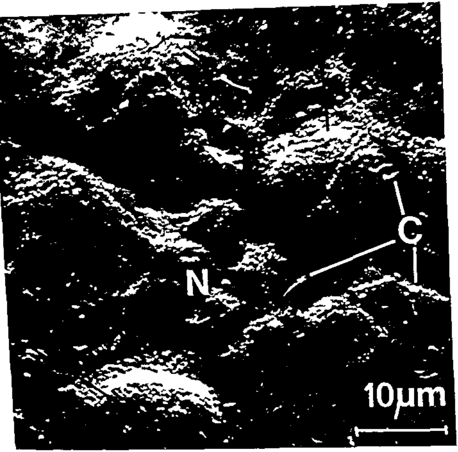


Fig 8
Detail of Zone III with Hassall Henle s warts HH The nuclei of the endothelial cells N tend to accumulate at the base of the warts Many cells have a centrally located cilium C The preparation was air dried from ether

shape and have less distinct borders than in other parts of the cornea This zone has a striped appearance (Fig 1) which appears to be due to circumferential subendothelial strands Trabecular cords often insert in Zone IV and may even extend into Zones III and II Isolated cords are seldom observed in Zones III and IV (Fig 7) Small oval or crescent like regions lack corneal endothelium and at such places one can sometimes observe subendothelial extensions of the trabecular meshwork Cilia are less frequent in Zone IV than in Zone II The cell borders and surface appear essentially the same as in Zones I and II

MONKEY CORNEA

In the monkey species investigated the corneas have an appearance similar to that in man There are some minor differences however Trabecular cords often run out for a considerable distance into the cornea especially in the cynomolgus (Macaca irus) and the stumptail monkeys (Macaca speciosa) Furthermore cilia are less abundant especially in the vervet monkey (Cercopithecus ethiops) and are strictly confined to Zones II and III Few Hassall Henle s warts were observed and border bars were seen only in the Rhesus monkey (Macaca mulatta) Thus the surface characteristics motivating a division of the peripheral part of the cornea into Zones III and IV are less apparent in monkeys than in human adult eyes

Discussion

The observations reported here indicate that rapid fixation after the circulation in the eye has ceased is a most important factor for good preservation of the surface ultrastructure of the cornea Marked post mortem changes develop within three hours in unfixed eyes The fixation and dehydration procedures used appear to have caused only slight shrinkage judging from the absence of graver artifacts such a cracks and cleavage of cell borders Dehydration may have influenced the varying degree of prominence of the cell nuclei in the different zones The general appearance of the endothelial cells with regard to shape size and number reported here is in good accordance with earlier findings by light microscopy and TEM (see Donn 1966 Ehlers 1966) The pleomorphism observed to develop with advancing age (Kaufmann et al 1966) was striking in all eyes from elderly patients Investigators using SEM (Spencer et al 1968 Tripathi 1969 Hager et al 1971 Hansson & Jerndal 1971) have reported on the general appearance of the inside of the human cornea but have refrained from describing structural details such as cilia microvilli border bars and surface pits

The division of the inside of the cornea into four zones in the present study seems justifiable from the surface characteristics Zone I includes the major part of the cornea and is characterized by low flat prominences due to the cell nuclei The most striking feature of Zone II is the abundance of ciliated cells Zone II contains Hassall Henle s warts and in Zone IV the cornea is again flat with subendothelial circumferential strands probably corresponding to the ring of Schwalbe Spencer et al (1968) divided the corneal endothelium into two parts the central cornea and a "zone S (S = smooth) corresponding to our Zone IV Hogan et al (1971) termed Zone S the "flat zone and further

more recognized a zone with Hassall Henle s warts corresponding to our Zone III Wolf (1968) in his study on monkeys introduced a three part division a prestomata region corresponding to our Zones II–IV the central region corresponding to our Zone I and between these two regions a transitional zone which he defined as the area of transition from non ciliated to ciliated endothelial cells In the present study we found no basis for dividing the monkey cornea into four zones due to the almost complete absence of Hassall Henle s warts (see below) and the greater extension of many trabecular cords out onto the cornea

Cilia or flagella on the endothelial cells of the cornea were first reported by Wolf (1968) using a wet replica technique in the Rhesus monkey (Macaca mulatta) Whether the correct term is cilia or flagella is not clear the structure is the same but the mode of operation differs (Sleigh 1971) The cilia were centrally located on the endothelial cells usually a single cilium per cell They were found only in the most peripheral part of the cornea Such cilia were not observed by Wolf in several other animal species investigated including the rabbit and the vervet monkey (Cercopithecus ethiops) The cilia could be seen only after autolytical removal of a superficial covering layer of viscous substance and Wolf suggested that the cilia mix this substance and depolymerizing enzymes In the present study cilia were observed in all the monkey species investigated including the vervet monkey In monkeys the distribution was similar to that reported by Wolf for Rhesus monkeys In humans however cilia were found in a much wider region only the central part of the cornea was almost devoid of cilia The size of the cilia described by Wolf agrees with that seen by us There is no doubt about the nature of the structures described as cilia or flagella we have observed these structures also with TEM (unpublished observations) Using TEM Hogan et al (1971) described cilia also on the corneal endothelium but found cilia on occasional cells only Our results suggest that the material they studied originated from the central part of the cornea since cilia are quite frequent in Zone II about 50 % of the cells have at least one cilium The function of the cilia – if any – remains to be established

The drop like structure on the surface of the endothelial cells which were observed in the present study seem analogous to the small type of microvilli described by Blumcke & Morgenroth (1967) on rabbit corneal endothelium The pits in the surface probably represent openings of pinocytotic vesicles first described in corneal endothelium by Donn (1961)

We could see no covering viscous layer on the posterior surface of the cornea in humans or monkeys Whether this is due to lack of the substance under normal conditions or loss of it during processing of the preparations is not

clear Nor have we observed any "pit-like islets" a depressed circular area of endothelial cell described by Wolf (1969) in all animals investigated except the rabbit and the Rhesus (Macaca mulatta) and vervet monkeys (Cercopithecus ethiops) Vrabec according to a personal communication to Wolf (1969) has observed "pit like islets" in humans by use of a replica technique The slit like or oval openings in the endothelial cover of the cornea in Zones III and IV seem analogous to the "prestomata" described by Wolf (1965) leading into the most anterior part of the trabecular meshwork. The cell borders of the endothelial cells show much interdigitation as is known from studies by TEM (see Donn 1966 Ehlers 1966) SEM (Blümke & Morgenroth 1967) and replica technique (Wolf 1966) As is also known from the studies by TEM (Blumcke & Morgenroth 1967) the ends of some digits appear to float freely in the aqueous humor The border bars do not seem to have been observed by TEM The nature of these structures is not clear It seems unlikely that the border bars are peripheral cilia since all such bars are oriented at right angles to the border line cilia would be expected to lie at random directions in processed specimens. It seems plausible that the border bars are related to the phenomenon of "leading lamella" and their projections are the "lamellopodia" described by Abercrombie (1971) in cell culture of fibroblasts

Hassall Henle s warts occur more often with advancing age a factor that may explain the rare occurrence in our monkey material as the animals were presumably young When warts occur outside Zone III the condition is known as cornea guttata and is observed in 6 % of adult humans (see Donn 1966) Those affected are considered unsuitable as corneal graft donors because of the danger of endothelial decompensation Corneas from eye banks with "traumatic" lines and more than 10 % disappearance of endothelial cells due to storage are also judged unsuitable Either of these conditions is observed in more than 30 % of corneal grafts from donors over 50 years of age (Kaufmann et al 1966) The measurement of corneal endothelium viability has recently been discussed by O Neill (1972) SEM offers a unique means of studying the endothelial surface structure and may be of clinical value in choosing suitable donor grafts Since the two corneas from one donor are identical in 95 % of the cases (Kaufmann et al 1966) one cornea can be used for structural investigation preoperatively while the other is retained for transplantation

Acknowledgments

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STUDY ON MORPHOLOGY AND FUNCTION OF THE DRAINAGE AREA OF THE EYE OF MAN

BY

A P NESTEROV and Y E BATMANOV

In meridional sections the anterior chamber angle is characterised by the width of the entrance into the angle, the shape of the apex, the configuration of the angle recess and the position of the anterior part of the ciliary body There are considerable variations in the morphology of the canal of Schlemm The most important characteristics of the canal include the position of the sinus as regards the apex of the anterior chamber angle, the width of its lumen and the inclination of the canal of Schlemm towards the anterior chamber The meridional portion of the ciliary body usually reaches the scleral spur However in some eyes the posterior attachment of the ciliary muscle is located behind the scleral spur

In some presumably normal eyes a partial blockage of the lumen of the Schlemm s canal was observed Blockage was achieved experimentally on isolated eyes of man by increasing the pressure in the anterior chamber The anterior position of the Schlemm s canal the narrow scleral spur and the posterior attachment of the ciliary muscle may be considered anatomical predispositions to blockage of the Schlemm s canal and the intertrabecular spaces

Key words anterior chamber angle – histology – aqueous

The drainage area of the eye contains the structures responsible for the outflow of the aqueous humor including the anterior chamber angle the trabecular meshwork the scleral spur the canal of Schlemm and its outlets the anterior part of the ciliary body and the iris root.

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The anatomy of the drainage system of the eye is well documented (Salzman 1912 Maggiore 1917 Dvorak Theobald 1934 1954 1959 Ashton 1951 Allen Burian & Braley 1955 Ashton Brini & Smith 1956 Flocks 1956 Brini 1959 Speakman 1959 1960 Unger & Rohen 1959 Twamoto 1967) However the individual peculiarities of the morphology of this area are very considerable and they have not as yet been studied completely The relationship between the different structures has not been described in detail The interrelationships between the function of the outflow system and the peculiarities of its morphology seem to be of great interest but have not as yet been studied well enough

The purpose of this paper is to present our data on the above mentioned subjects

Material and Method

One hundred cadaver eyes of 100 persons aged 24 to 82 were taken between 12 and 24 hours after death In all cases death was sudden After fixation of the eyeballs in a 5 % formalin solution they were cut at the level of ora serrata Celloidin embedded blocks of the anterior part of the eye were prepared Sagittal sections were cut and stained with hematoxylin and eosin and by the Van Gieson and the Mallory methods The measurements of various parameters of the area were performed with the ocular micrometer

To determine the outflow facility 38 cadaver eyes were perfused with barbiturate buffer solution (pH 7 5) A hypodermic needle connected with the perfusion system was introduced through the sclera first into the posterior chamber and then through the pupil into the anterior chamber The outflow facility was measured under the pressure of 30 cm H O (22 mmHg)

To observe the changes in the width of Schlemm s canal under the influence of high intraocular pressure five cadaver isolated eyes were perfused with 5 % formalin solution during 4–24 hours The perfusion pressure was equal to 66 mmHg The fellow eyes were also perfused with the formalin solution during the same period of time but at a perfusion pressure of 22 mmHg All the eyes were examined histologically

In order for us to observe visually the blockage of Schlemm s canal on 20 of the 30 eyes perfused the experiments were more complicated and included lamellar resection of perilimbal scleral tissue The experiments were performed as described in an earlier publication (Nesterov 1970) The drainage area of all the perfused eyes was then examined histologically

Results

In sagittal sections the anterior chamber angle is characterized by the following features the width of the entrance into the angle the shape of its apex the configuration of the angle recess and the position of the anterior part of the ciliary body

There are three types of apex having a sharp a medium or an obtuse angle The apex is shaped by the insertion of the iris root into the ciliary body If the insertion is anterior the shape of the apex is sharp (Fig 1) posterior insertion of the iris root causes an obtuse apex (Fig 2)

In the upper segment of the angle a sharp apex was observed in 33 % of



Fig 1
The sharp apex of the anterior chamber angle and the middle position of Schlemm s canal (Van Gieson stains × 64)

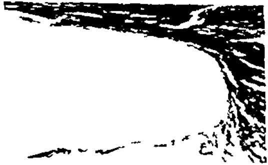


Fig 2
The obtuse apex of the anterior chamber angle (Van Gieson stains × 64)



Fig 3
Additional recess in the angle of the anterior chamber (Van Gieson stains × 64)

the eyes examined a medium apex occurred in 60 % and an obtuse apex in 7 % In the inferior segment an obtuse apex is more frequent (29 %) a sharp apex was observed in only 9 % of all cases These differences are statistically significant ($P < 0.003$)

In most eyes (69 %) the iris root gradually passes into the iris itself and in the meridional section the anterior chamber angle has an even configuration (Fig 1) In 31 % of the eyes examined the iris root was very thin and a sharp border could be observed between the iris and its root In such eyes one can observe an additional recess in the posterior wall of the anterior chamber (Fig 3)



Fig 4
The anterior part of the ciliary body has an inward turn and forms the posterior wall of the chamber angle (Van Gieson stains × 64)

Table I

The *sizes of* various structures in *the* drainage area of a hundred eyes

The structure	Upper segment		Lower segment		Both segments	
	Mean	S D	Mean	S D	Mean	S D
1 *Diameter* of trabeculae	640	132	619	134	630	134
Thickness of trabeculae	105	27.6	120	34.2	113	39.0
3 Length of scleral *spur*	85.7	57.6	94	60.9	89.5	59.8
4 Thickness of iris root	136	51.5	148	54.0	149.0	58.1
5 Diameter of Schlemm's canal	382	100	360	94	371	98
6 Distance between the posterior end *of* Schlemm's *canal and the apex of* chamber angle	28.5	88.8	29.5	83.4	29.0	87.0
7 Width of the *lumen of* Schlemm's canal	24.9	14.3	25.4	13.9	25.2	14.1
8 *Angle* of inclination of Schlemm's canal towards *the anterior* chamber (degrees)	12.6	7.7	12.2	7.2	12.4	7.5

All values *but the angle* of inclination of Schlemm's canal are given in microns

In some eyes the anterior part of the ciliary body has an inward turn and participates in forming the posterior wall of the anterior chamber (Fig 4) This phenomenon was observed in 9 % of the cases

The sizes of different structures in the drainage area of the eye are given in Table I The thickness of the trabeculum was measured at the level of the centre of the scleral sinus The diameter of the scleral spur was measured from its tip to the level of the posterior end of Schlemm s canal To measure the width of the lumen of Schlemm s canal the latter was divided into four equal parts and measurements were taken at the border of each part The average width of the lumen was calculated from these three measurements

In the inferior segment of the eye the trabeculum was shorter and thicker than in the superior segment This difference is significant ($P < 0\ 003$)

There were considerable variations in the position of Schlemm s canal as regards the apex of the anterior chamber angle We classified the variants into three groups – anterior middle and posterior positions If the first position occurred the apex of the chamber angle was situated behind the Schlemm s canal (Fig 5) The largest distance between the posterior end of the scleral sinus and the apex was equal to 300 μ In the middle position the posterior end of the canal of Schlemm and the apex are at the same level (Fig 1) If part of Schlemm s canal lies behind the apex the position of the canal is considered to be posterior (Fig 6) The largest distance between the posterior end of the canal of Schlemm and the apex was 200 μ

Our data concerning the position of Schlemm s canal are summarised in Table II



Fig 5

The anterior position of Schlemm s canal with two lumens The tip of the ciliary muscle (arrows) is far behind the posterior end of the canal of Schlemm (Van Gieson stains × 64)



Fig 6
The posterior position of the canal of Schlemm (Van Gieson stains × 64)

The inclination of the lumen of Schlemm's canal towards the anterior chamber varied from 0 to 40 More often the slope was 10–15° The scleral sinus usually had a single lumen in each section although two or more lumens were observed in 20 segments of 13 eyes (Fig 5)

In most eyes examined the ciliary muscle was attached to the scleral spur and to the uveal portion of the trabecular meshwork (Fig 7) In 26 segments of 20 eyes (20%) the tip of the meridional portion of the ciliary muscle did not reach the scleral spur and was attached behind the latter to the sclera (Fig 5)

Table III shows correlation coefficients between various parameters in the drainage area of the eye The width of the lumen of Schlemm's canal to some extent seems to be an index of the functional state of the outflow system The data presented in Table III indicate that the wider the lumen of the canal of Schlemm the greater is the C value and the more developed is the scleral

Table II
The position of Schlemm's canal in a hundred eyes

Position of Schlemm's canal	Upper segment	Lower segment	Both segments
Anterior	3	49	81 (40.5%)
Middle	5[illegible]	31	8[illegible] (41%)
Posterior	1	[illegible]0	37 (18.5)



Fig 7
The ciliary muscle (c m) is attached to the scleral spur and to the uveal part of the trabecular meshwork (Van Gieson stains × 64)

spur the position of Schlemm's canal being more posterior and the angle between the canal and the anterior chamber tending to be less

In eyes with the ciliary muscle attached posteriorly the width of the lumen of Schlemm's canal was equal to 10 6±5 8 μ (mean±S D) This is 2 8 times less than the other eyes examined This difference is significant (P < 0 001)

Table III
The values of the coefficients of correlation (r) between various parameters of the drainage area of the eye (100 eyes 200 segments)

Correlation between	r	S D
(1) Diameter of trabeculae and of Schlemm's canal	+ 0 610*	0 064
(2) Width of the lumen of Schlemm's canal and		
(a) diameter of the canal	+ 0 150	0 099
(b) length of scleral spur	+ 0 353*	0 088
(c) distance between the posterior end of the canal and chamber angle apex	— 0 305	0 0[illegible]
(d) angle of the inclination of Schlemm's canal towards the anterior chamber	+ 0 32 *	0 090
(e) C value obtained by perfusion (58 eyes 22 mmHg)	+ 0 419*	0 13

* The value of the coefficient is statistically significant



Fig 8
The blockage of the anterior part of the canal of Schlemm (Van Gieson stains × 140)

Partial blockage of Schlemm s canal was observed in 28 segments of 20 eyes The blockage was found in the upper segment in 7 eyes in the lower segment in 5 eyes and in both segments in 8 eyes The anterior portion of the canal of Schlemm was usually compressed (Fig 8)

In eyes with partial blockage of Schlemm s canal as compared with all the eyes investigated the canal was situated more anteriorly the scleral spur was

Table IV
Mean values of s me parameters in 20 eyes (28 segments) with the partial blockage of Schlemm s canal and in all eyes of the series (100 eyes 200 segments)

Parameters	$M_1 \pm m_1$	$M \pm m$	P
1 Diameter of trabeculae	657 ±3?0	630 ±13 5	>0 1
2 Thickness of trabeculae	103 ± 5 7	113 ± 3.2?	>0 1
3 Length of scleral spur	69 8± 9 5	89.5± 6 0	<0 05
4 Diameter of Schlemm s canal	39 ±?1 4	371 ± 9 9	>0 1
5 Distance between the posterior end of the canal and the chamber angle apex	80 ±17 1	29 ± 8 ?4	<0 01
6 Width of the lumen of Schlemm s canal	1? 7± 1 48	?5 ?± 1 42	<0 001
Angle of inclination of Schlemm s canal (degrees)	5 9± 1 06	1? 4± 0 75	<0 001

M_1 m_1 = the mean and its error in the eyes with partial blockage of Schlemm s canal
$M + m$ = the mean and its error in all eyes of the series All values but the angle of inclination of Schlemm s canal are given in microns

less well developed, and the angle of the inclination of the scleral sinus towards the anterior chamber was less (Table IV) These differences were significant

The results of perfusion experiments on 20 cadaver eyes (19 persons) after perilimbal lamellar sclerectomy can be subdivided into three groups In five eyes the blockage of Schlemm s canal was not observed while pressure in the perfusion system rose from 22 to 66 mmHg The second group consisted of 3 eyes (2 persons) in which the blockage of Schlemm s canal could be observed before the eyes were connected with the perfusion system The third group includes 12 eyes in which sinus blockage appeared while pressure in the perfusion system and the anterior chamber was rising

The first group of eyes was characterised by the high C values (the average was 0 362 mm³/minute per mmHg) the weak pigmentation of the trabeculae and a well developed scleral spur The mean diameter of the latter was equal to 133 μ In four eyes Schlemm s canal was in the posterior position and in one eye it was in the middle position

In the second group the C values were low (0 11–0 19 mm³/minute per mmHg) the pigmentation of the trabeculae was intensive the scleral spur was very narrow (the average was equal to 20 μ) and Schlemm s canal was in the anterior position

In the third group of eyes the C values varied from 0 25 to 0 42 mm³/minute per mmHg the pigmentation of the trabeculum was moderate and the mean diameter of the scleral spur was 65 μ The canal of Schlemm s was in the anterior position in six eyes and in the middle position in six eyes The

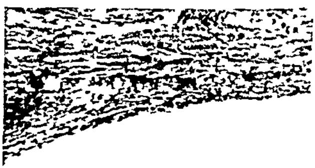


Fig 9

An artificial blockage of the canal of Schlemm (arrows) The eye was perfused with 5 % formalin solution during 4 hours Perfusion pressure was 66 mmHg (Van Gieson stains × 140)



Fig 10
An artificial blockage of the canal of Schlemm (arrows) The eye was perfused with 5 % formalin solution during 24 hours Perfusion pressure was 66 mmHg (Van Gieson stains × 140)

blockage of Schlemm s canal occurred when the pressure in the anterior chamber (P_{bl}) was raised to 40–66 mmHg (the mean was 54 8 mmHg) During the blockage the C values decreased by 36–59 % The visible split between the inner and the outer walls of Schlemm s canal appeared only when the pressure in the anterior chamber was lowered to 32–62 mmHg ($P_{d\,bl}$) The mean difference between P_{bl} and $P_{d\,bl}$ was equal to 6 8 mmHg

In all the eyes which were perfused with the formalin solution under the pressure of 66 mmHg the blockage of Schlemm s canal was discovered upon histological examination (Fig 9 and 10) The canal of Schlemm was open in the second eyes which were perfused under a pressure equal to 22 mmHg

Discussion

The size of the structures in the drainage area of the eye and the interrelationship between them can be changed under the influence of fixation of embedding into celloidin and of the section of the tissue Although it seems unlikely that these changes were large enough to influence the results of this investigation it is impossible to ignore them completely

It is well known that the narrow angle of the anterior chamber is predisposed to angle closure glaucoma This seems to be true also for the sharp apex of the anterior chamber If a sharp apex is found in combination with a posterior

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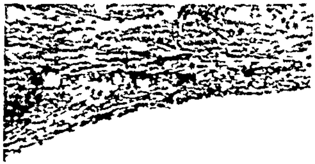


Fig 9

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position of the Schlemm s canal the slightest displacement forward of the iris root may be sufficient to block the aqueous outflow

The additional recess in the anterior chamber angle is in combination with a very thin iris root One may speculate that in eyes with the relative pupil block the thin iris root can be easily displaced forward and pressed against the scleral spur and the trabeculum This is probably a condition predisposing to the shortening of the anterior chamber angle

If the the anterior part of the ciliary body is turned inward and forms the peripheral portion of the posterior wall of the chamber angle it is in danger of being injured during iridectomy After filtering operations this part of the ciliary body can probably be incarcerated in the scleral wound blocking the fistula

In the living eye there is a tendency to narrow the trabecular spaces and especially Schlemm s canal because of the pressure difference in these structures and the anterior chamber The mechanism "ciliary muscle scleral spur trabeculum" maintains the trabecular spaces and the canal of Schlemm in the open state and prevents their collapse The efficiency of this mechanism depends on the interrelationship between the positions of Schlemm s canal and of the ciliary muscle The greater the distance between these structures the less the effect of the mechanism on the trabeculum and Schlemm s canal

Therefore the anterior position of Schlemm s canal the short scleral spur and the posterior attachment of the ciliary body may be considered anatomical predispositions to the blockage of Schlemm s canal and the trabecular spaces It was suggested elsewhere (Nesterov 1970) that blockage of the canal of Schlemm is a link in the pathogenesis of primary open angle glaucoma Consequently one may suppose that the anatomical features mentioned above predispose to this type of primary glaucoma

The partial blockage of Schlemm s canal was observed in some normal eyes This might be an artificial change however in three isolated eyes blockage of the canal of Schlemm was found after lamellar sclerectomy These eyes were treated only by glycerol The findings were confirmed by the following histological examination

In isolated eyes the blockage of Schlemm s canal and the trabecular spaces can be produced artificially by increasing the pressure in the anterior chamber If this is true for living eyes one may suggest that the long standing increase of the intra ocular pressure can impair the Schlemm s canal and the trabecular meshwork This might be the cause of the transformation of the so called hypersecretion glaucoma into the retention open angle glaucoma

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THE VALUE OF PHOTOCOAGULATION IN DIABETIC RETINOPATHY

BY

BIRGITTA ZETTERSTRÖM

Photocoagulation was carried out on 80 patients with bilateral symme trical diabetic retinopathy whose ages ranged from 21 to 70 years Only one eye was treated in each case and the response was compared with the condition of the untreated fellow eye The degree of severity of retinopathy varied changes such as microaneurysm retinal oedema yel low exudate dilated blood vessels retinal neovascularisation not involv ing the vitreous and intra retinal and preretinal haemorrhages were present Cases which showed formation of new vessels or connective tissue proliferation into the vitreous were excluded
The follow up period varied from 1 to 3 years All patients were fol lowed up with fundus photographs in colour estimation of visual acuity and fluorescein angiography These procedures showed a clear cut re mission of retinopathy in 68% of the cases no improvement in 26% and progress on of the lesions in 10% As regards the situation in the un treated fellow eye the corresponding percentages were 14 71 and 15% respectively

Key words diabetes – diabetic retinopathy – photocoagulation

During the past ten years photocoagulation has been used increasingly in the treatment of diabetic retinopathy Meyer Schwickerath was the first to give the procedure a trial in the years 1955 to 1959 (Meyer Schwickerath 1959

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rely on a comparison of the clinical appearance as shown by the fundus photo graphs as an index of improvement rather than on alteration of visual acuity which was good in the majority of the cases before as well as after the treat ment

The apparatus used was the West German Zeiss coagulator

Each patient was treated on two or three occasions producing about 100 photocoagulation lesions each treatment and using the 3 or 4 5° apertures

All patients were followed up for one to three years

Results

The fundus photographs taken before photocoagulation and after a follow up period of one to three years after the treatment were studied carefully and the findings compared with the condition of the untreated fellow eye in each case On the basis of these findings the cases were grouped into three groups as fol lows cases showing improvement cases showing no change and cases showing progression of the retinopathy

The condition of the treated eye was compared with that of the untreated fellow eye in each case (Table I) The findings were as follows in 68 % of

Table I

Comparison of the clinical course of retinopathy in the treated and untreated fellow eye.

	Improvement	No change	Progression
	Treated eyes		
Male (38)	26 (68 %)	10 (26 %)	2 (6 %)
Female (4)	25 (60 %)	11 (26 %)	6 (14 %)
	Untreated fellow eyes		
Male (38)	5 (13 %)	28 (74 %)	5 (13 %)
Female (42)	6 (14 %)	29 (69 %)	7 (17 %)

1968) Subsequently several investigators have published cases successfully treated by this method (Moura Brasil & de Rezende 1961 Okun & Cibis 1966 Okun 1968 Wetzig & Jepson 1966 1967 1968 Amalric & Biau 1967 Guillaumat 1968 Schott 1965 Wessing & Meyer Schwickerath 1969) In 1971 Irvine & Norton published a series of 34 cases of retinopathy with symmetrical involvement of both eyes in which only one eye was treated by photocoagulation The treated eye improved markedly in some cases but spontaneous remission in the untreated fellow eye was also observed They concluded from their observations that the therapeutic value of photocoagulation was questionable in the treatment of at least some diabetic retinopathies but that there for use of the procedure is justified in some cases

In order to assess the therapeutic value of photocoagulation in diabetic retinopathy only one eye of 80 patients with bilateral symmetrical involvement was treated and the condition of the untreated fellow eye was compared with that of the treated eye in each case

Material and Methods

The present series comprised 80 cases of bilateral symmetrical diabetic retinopathy treated with photocoagulation 38 being men and 42 women their ages ranged from 21 to 70 years The degree of severity of the condition varied changes such as microaneurysm retinal oedema yellow exudate dilated blood vessels retinal neovascularisation not involving the vitreous and intra retinal and preretinal haemorrhages were present Cases which showed neovascularisation or proliferation of connective tissue into the vitreous were excluded

In order to assess the therapeutic value of photocoagulation only one eye of the patients in this series was treated and the response in each case was compared with the condition of the untreated fellow eye If the severity of retinopathy was not symmetrical the fundus showing the more extensive changes was treated

Before treatment was begun the condition of the fundus was recorded by serial photographs in colour and visual acuity was examined In addition fluorescein angiography was carried out on the eye selected for treatment All the patients were systematically followed up by these procedures and this permitted an assessment to be made of the clinical course of the retinopathy As a rule visual acuity was good ranging from 0 6 to 1 0 in 78 patients In only 4 cases was the visual acuity found to be less than 0 5 in the treated eye When subsequently assessing the effect of the treatment one had therefore to

Table III

Classification of the patients into two groups without reference to sex

	80 cases	
Age	21–50	51–70
Improvement	46 (71 %)	5 (33 %)
No change	12	9
Progression	7	1
Total	65	15

COMPLICATIONS

Haemorrhage occurring within three weeks of photocoagulation was considered to be a complication of the procedure In 3 cases haemorrhage occurred within this period of time in 2 of them complete absorption occurred within six to eight weeks after treatment A moderate reduction of the visual field was noted in the majority of the treated patients However only in exceptional cases had it decreased to such an extent that the patient was conscious of it

Judging from the favourable results achieved with photocoagulation in the treatment of diabetic retinopathy in the cases in this series and considering the few cases in which a complication attributable to the treatment was observed there is justification for using this technique although it appears to produce only symptomatic relief However it is important to select carefully the cases which from experience gained in this field appear to be suitable for treatment by photocoagulation and to follow up for a prolonged period of time the patients thus treated

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the male patients retinopathy had improved the corresponding percentage in the female patients was 60 % In 26 % of the female patients and male patients respectively retinopathy showed no change and in 6 % of the men and 14 % of the women it had progressed A comparison of these findings with the situation in the untreated fellow eye showed remission of retinopathy in only 13 % of the male patients and only 14 % of the female patients in 74 % of the men and 69 % of the women it showed no change

Table II shows the classification of the male and female patients respectively into five age groups each group covering a ten year period However these groups were found to be too small to permit drawing definite conclusions about a possible relationship between the patient s age and the effect of photo coagulation For this reason the patients were re classified into two age groups without reference to sex one group including the patients aged 21 to 50 years and the other those aged 50 to 70 years (Table III) This Table shows that in 71 % of the younger and in 33 % of the elderly patients retinopathy had improved One is therefore inclined to believe that more favourable results are achieved with photocoagulation in young patients

Table II
Classification of the male and female patients respectively into five age groups

Male (38)					
Age	21–30	31–40	41–50	51–60	61–70
Improvement	5	7	11	3	–
No change	2	2	2	2	2
Progression	1	1	–	–	–
Total	8	10	13	5	2

Female (42)					
Age	21–30	31–40	41–50	51–60	61–70
Improvement	13	7	3	1	1
No change	2	3	1	4	1
Progression	2	2	1	–	1
Total	17	12	5	5	3

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SIMPLE MANOMETRIC PROCEDURE FOR TEAR PATHWAYS

BY

IMRE KORCHMÁROS

We introduced into both canaliculi and the nasal cavity a cannula which was connected to a manometer by a rubber pipe The air pressure could be directed away from the nasal cavity by pressing and sucking the air at held nostrils and away from the tear ducts by injecting air through the wall of the rubber pipe In addition to the examination of the physio logical v riat ons (t what suction and pressure the valves close etc) the method could be used also to determine the mechanism of certain patho log cal conditions

Key words manometric procedure – tear (lacrimal) pathway – epiphora – ethmoiditis

Data on the manometric procedure for studying tear pathways have already been published by among others Rosengren & Kugelberg (1935) Nagashima (1954 1958) Brienen & Snell (1969)

To examine air pressure alterations and their effects on the nasal cavity and the tear pathways as well as on post operative new ducts we assembled a simple device consisting of a spring manometer which we connected to a 0 6 mm cannula be means of a rubber pipe The cannula of such a device was

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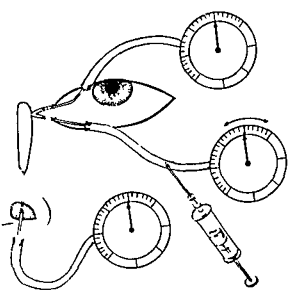


Fig 1
The scheme of the manometric procedure for the tear pathway

introduced into the upper canaliculus another into the lower one and a third into the nasal cavity via the nostril blocked by a wet tampon (Fig 1)

The air pressure in the nasal cavity was altered by forced expiration and inspiration at held nostrils while that of the tear pathways was altered by injecting and aspirating air via a hypodermic needle through the wall of the rubber pipe which was placed in the canaliculus

This procedure was applied not only for determining at what suction and pressure the valves close and whether the walls of the sac or those of the canaliculus adhere etc but also for determining the mechanism of certain pathological conditions

In one case dacryocystorhinostomy failed to eliminate the epiphora and patency was still restricted even after probings The pointer of the manometer connected to the common punctum of the canaliculi also traversed for both suction and pressure effects but soon it stopped because the end of the cannula was filled by discharge The effect of the injected air through the tear pathway reached the nasal manometer only irregularly with halts

Our supposition that the discharge blocking the new duct probably was derived from ethmoiditis was confirmed by the reoperation After the affected ethmoidal cells were removed through the enlarged osseous flap the tear pathway became permanently patent and the epiphora ceased

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EXPERIMENTAL OBSERVATIONS ON THE ECHOGRAMS OF THE OPTIC NERVE AND ON THE EFFECTS OF SOME TISSUES UPON THEM

BY

ARVO OKSALA MOHAMMED ALI HADIDI and SIRKKA LIISA JÄÄSLAHTI

The optic nerve of the pig was investigated experimentally with A and B scans in plain water and surrounded by the retrobulbar tissues and muscles The effects of some tissues upon the nerve were also studied In homogeneous medium substance i e water the optic nerve was acoustically heterogeneous in both A and B scan In B scan the centre of the optic nerve was acoustically homogeneous when surrounded by retrobulbar tissues and muscles while in A scan the optic nerve was acoustically heterogeneous The position direction and anatomical structure of the optic nerve as well as the fact that the change in acoustic impedance is only slight between the optic nerve and the surrounding tissues may be some of the reasons why the optic nerve appears as an *acoustically* empty space in clinical B scan examination

Key words ultrasonography echogram – optic nerve – retrobulbar tissue

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Present information on the echograms of the optic nerve in both A and B scans is very scarce The optic nerve has usually been observed in a B scan picture where one can see its shadow in the middle of echoes reflected by retrobulbar tissues mainly muscle and fat (Baum 1965 Baum & Greenwood 1958 1960 Purnell 1966 1969) Upon B scan examinations echoes have normally been obtained from a depth of 10–15 mm in the retrobulbar space

The purpose of this study is to clarify experimentally the acoustic structure of the optic nerve in both A and B scans and to investigate the effect of some tissues mainly muscle tissue on the echograms of the optic nerve

Material and Methods

The apparatus used for the investigation was Kretztechnik s ultrasonic equipment model 7100 MA and an 8 MHz/5 mm transducer which was slightly focused With the amplification that was used the diameter of the focusing area was 2 5 mm During B scan examinations the movement of the transducer was linear the examinations taking place in a water bowl into which the transducer was immersed The tissues that were being examined were placed beneath the transducer on a copper wire stand The distance of the transducer from the optic nerve under examination was 25–27 mm For the examinations we used the maximum amplification of the equipment i e db reserve = 80

Eyes and retrobulbar tissues from newly slaughtered pigs were used The optic nerve was examined alone so that a 15 mm long piece of the optic nerve was attached to a scleral rear wall calotte The diameter of the optic nerve was 3–3 5 mm A 15 mm long tissue particle was prepared from the retrobulbar tissues This piece contained 5 mm of plain optic nerve and 10 mm of retrobulbar tissue consisting of the optic nerve surrounded by fat and muscular tissue A situation where the optic nerve was surrounded by muscle tissue alone was created by tying some retrobulbar muscle tissue around a separate optic nerve When the effects of some tissues on A and B scan echograms of the optic nerve were investigated we used extrinsic eye muscle tissue the sclera and the choroid The test particle we used was a 5 mm long piece of the sclera

The following examinations were made (1) A B scan echogram of the optic nerve was examined in the situation where a 15 mm long piece of the optic nerve was attached to a scleral rear wall calotte (2) A and B scan echograms of the optic nerve were examined in cases where the sound beam first hit the optic nerve alone and then the part of the nerve which was surrounded by retrobulbar tissues A B scan echogram was also examined in a situation where



Fig 1
A B scan echogram of a scleral rear wall calotte with the optic nerve attached to it Both the sclera and the optic nerve are acoustically heterogeneous

some extrinsic eye muscle tissue had been tied around a separate optic nerve (3) A separated optic nerve and a piece of the sclera were placed on the copper wire stand and B scan pictures were taken of them Then we examined the effects of extrinsic eye muscle the sclera and the choroid on this particular B echogram by placing these particles on the optic nerve and the piece of sclera so that the tissues touched each other

Results

All the situations that were mentioned above were examined 10 times The results which will be presented in the form of echograms were easily repeatable.

B-scan echogram of the optic nerve attached to a scleral calotte

Fig 1 represents a typical examination result The optic nerve which is attached to a scleral calotte is seen as a fairly coherent bar consisting of light points In this B scan examination the optic nerve is acoustically so heterogeneous that almost its entire area reflects registrable echoes like the sclera

A and B scan echograms of the optic nerve surrounded by retrobulbar tissues and extrinsic eye muscle

Fig 2 A shows a B scan echogram of the plain optic nerve which is sticking out of retrobulbar tissue on the copper wire stand The optic nerve is rep

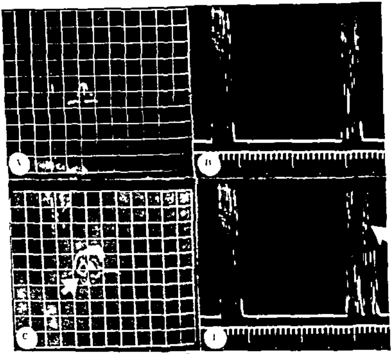


Fig 2

2 A represents a B echogram of the plain optic nerve 2 B the corresponding A echogram 2 C shows the optic nerve (arrow) surrounded by retrobulbar tissues 2 D presents an A echogram of a case where the sound beam has travelled through the retrobulbar tissues and the optic nerve (arrow)

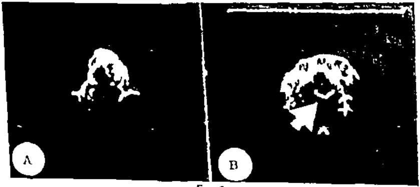


Fig 3

B scan echograms of a tissue particle which contained the optic nerve surrounded by extrinsic eye muscle tissue In 3 A the optic nerve cannot be distinguished from the surrounding tissues but in 3 B it can be seen (arrow)

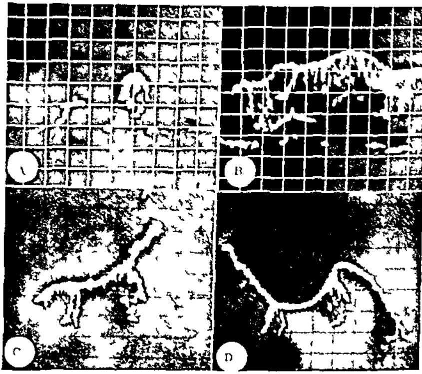


Fig 4

The effects of some tissues on the B scan echograms of the optic nerve and a piece of sclera In 4 A one can see the echograms of the optic nerve (on the right) and the piece of sclera In 4 B extrinsic eye muscle tissue prevents the observation of the optic nerve and the piece of sclera In 4 C and 4 D a sclera and a choroid make it difficult to see the optic nerve and the piece of sclera

resented by an arc resembling a semi circle and some echoes are also reflected from inside the optic nerve The corresponding A scan echogram can be seen in Fig 2 B In this examination the optic nerve appears to be acoustically even more heterogeneous than in B scan Fig 2 C presents an acoustic cross section of the optic nerve when it is surrounded by retrobulbar tissues The optic nerve which is represented by a circle of light points is clearly distinguishable from other tissues (arrow) Fig 2 D shows an A scan picture of retrobulbar tissues at the points of the optic nerve Even if the centre of the optic nerve is represented by an acoustically empty space in B scan the same area is altogether quite heterogeneous in A scan (arrow)

At a B scan examination it was not always possible to localize the optic nerve quickly among the retrobulbar tissues the success of the search being very critically dependent on the direction of the sound beam in relation to the optic nerve At a perpendicular A scan examination the localization of the optic nerve was easier than in B scan When we tried to localize with B scan

the optic nerve which had been surrounded by extrinsic eye muscles we usually obtained an echogram like the one in Fig 3 A There one can see echoes reflected by muscle tissue but no distinct optic nerve By changing continuously the direction of the sound beam in relation to the optic nerve an echogram like the one in Fig 3 B could be obtained There one can distinguish the optic nerve surrounded by muscle tissue (arrow) The centre of the optic nerve is a ain acoustically empty

The effects of muscle tissue the sclera and the choroid on a B-echogram of the optic nerve and a piece of sclera

Fig 4 A represents a B scan picture of the optic nerve and a piece of sclera on the copper wire stand The optic nerve is on the right Echoes can be registered from its centre The echogram in Fig 4 B represents a situation in which a thin layer of extrinsic eye muscle tissue covered the optic nerve and the piece of sclera The echoes from the optic nerve and the sclera were usually mixed up with the echoes of the muscle tissue to such an extent that in B scan it is generally impossible to distinguish these two tissues from muscle tissue Fig 4 C is from a situation where a long scleral tissue is in contact with the optic nerve and the piece of sclera In Fig 4 D these two tissues are in contact with the choroid Even very thin tissues like the sclera and the choroid make it difficult to find the optic nerve in B scan if they are in contact with the nerve

Discussion

When a plain optic nerve is examined in an acoustically homogeneous medium substance i e water the optic nerve proves to be acoustically heterogeneous in both A and B scan in other words it reflects a large number of echoes

The sheets covering the optic nerve and the nerve fibers lie to a large extent, parallel to one another while the surrounding retrobulbar tissues contain very many acoustic border surfaces which point in various directions When the retrobulbar space is examined with present ultrasonic equipment the sound beam always hits perpendicularly several border surfaces in the tissues surrounding the optic nerve while the optic nerve itself is always hit more or less slantingly and therefore the sound beam reflects and refracts in the area of the optic nerve The optic nerve is thus both anatomically and acoustically more homogeneous than the surrounding tissues This may explain the fact that in B scan the optic nerve often appears as an acoustically empty space

According to our observations several even thin tissues make it difficult to

discover the optic nerve if they are in immediate contact with it especially in B scan This is due to the fact that there is only slight difference in acoustic impedence between these tissues and the optic nerve

On the basis of what has been said above it seems obvious that at least in the early stages ultrasonic diagnosis of tumours in the optic nerve is not easy because the acoustic border surfaces inside the tumour tissue also point in various directions in the same way as in the retrobulbar tissues which surround the optic nerve

The results that have been presented here show that in B scan the centre of the optic nerve was acoustically homogeneous both in the retrobulbar space and when surrounded by muscle tissue while in A scan the whole nerve was acoustically heterogeneous With the equipment that we used A scan was definitely more sensitive than B scan

At clinical examination B scan is better than A scan for finding and localiz ing the optic nerve This is due to the position and direction of the optic nerve because in A-scan the sound beam cannot be directed perpendicularly to the nerve

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LATE RECURRENCE OF RETINOBLASTOMA

BY

JAN YTTEBORG and KRISTEN ARNESEN

A case is presented with recurrence of retinoblastoma in a 14 year old girl 12 years after irradiation treatment The first eye had been enucleat ed for the same diagnosis at the age of 1 months In the differential d agnosis between an inflammatory and a neoplastic condition in the eye cytologic examination of material aspirated from the anterior chamber appeared useful

Key word retinoblastoma

A case is presented of bilateral retinoblastoma with intraocular recurrence in the conservatively treated eye after 12 years The case also demonstrates the usefulness of diagnostic cytology in ophthalmology

Case History

The patient is a gi l born in April 19 5 No family history of retinoblastoma In 19 6 when 1 months old the child was adm tted to the University Eye Clinic Rikshospi talet with the diagnosis of bilateral retinoblastoma The right eye was observed to be f lled w th tumour masses and was enucleated Histopathological examination verified the diagnos s

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discover the optic nerve if they are in immediate contact with it especially in B scan This is due to the fact that there is only slight difference in acoustic impedence between these tissues and the optic nerve

On the basis of what has been said above it seems obvious that at least in the early stages ultrasonic diagnosis of tumours in the optic nerve is not easy because the acoustic border surfaces inside the tumour tissue also point in various directions in the same way as in the retrobulbar tissues which surround the optic nerve

The results that have been presented here show that in B scan the centre of the optic nerve was acoustically homogeneous both in the retrobulbar space and when surrounded by muscle tissue while in A scan the whole nerve was acoustically heterogeneous With the equipment that we used A scan was definitely more sensitive than B scan

At clinical examination B scan is better than A scan for finding and localizing the optic nerve This is due to the position and direction of the optic nerve because in A scan the sound beam cannot be directed perpendicularly to the nerve

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fixed and stained according to the Papanicolaou method and studied in the Depart ment of Pathology The finding of malignant cells was reported

During the following days the inflammatory signs and tension increased the patient had considerable pain in the eye and the function was rapidly failing Consequently the eye was enucleated April 14 19F9 and sent to the pathologists for examination

Exfoliative Cytology

The smear from the anterior chamber showed clusters of cells the majority of which were not well preserved some of them being necrotic. A certain number of relatively well preserved cells was present however They were slightly larger than mature lymphocytes The cytoplasm was scanty and most of the nuclei appeared naked They were round to oval varying slightly in size with a punctate chromatin structure and usually a well defined nuclear mem brane (Fig 1) Nucleoli were usually indistinct The nuclear structure clearly differed from that of lymphocytes In addition groups of neutrophile granulo cytes were present

The predominating cells in the smear were interpreted as malignant neo plastic cells which were well compatible with retinoblastoma The possibility of a purely inflammatory exudate was rejected

Histopathology

The enucleated specimen was fixed in 4 % unbuffered formaldehyde solution The globe measured 22 × 23 mm. A cloudy exudate was seen in the anterior chamber The upper and lower cups were cut off In the upper section plane no definite tumour could be recognized macroscopically but the retina showed some variation in thickness In the lower section plane the retina was irregu



Fig

The enucleated left eye cut horizontally below the optic nerve and limbus 1 1

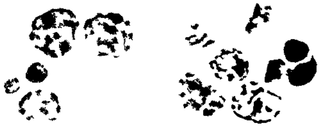


Fig 1
Retinoblastoma cells in smear of aqueous aspirate. Papanicolaou stain × 1970

In the left eye a tumour was found 2–3 disc diameters above the disc prominating 5–6 D and 2–3 disc diameters wide X ray treatment was given in a total dose of 6250 rad from the left temporal region and 5550 rad from the right orbit The tumour showed signs of regression but one year later in 1957 the patient was readmitted to the hospital with findings indicating active tumour growth at the same site in the eye ground She was again treated with deep X ray on the same two fields as previously with a total dose of 3100 rad on each At this time obvious signs of irradiation damage of the skin occurred and according to the radiologists opinion no further deep X ray treatment was possible The tumour now showed little evidence of regression and three months later in December 1957 the patient was treated in London by implantation of a ^{60}Co disc (Mr Stallard) Following this treatment a typical flat white post irradiation scar appeared corresponding to the tumour site Two years later in 1959 a small recurrence at the border of the scar was suspected and this area was light coagulated by Mr Stallard

During the following years there were no signs of recurrence Some small punctate haemorrhages were seen in the posterior pole and 5 years after the last treatment a circinate retinopathy developed close to the macular region These findings were considered to represent late complications of the therapy given probably caused by the irradiation damage to the choroidal and retinal vessels In addition a posterior cortical cataract developed The patient had a visual acuity of about 5/20 and she attended ordinary school without any difficulty

In April 1969 when she was 14 years old and 10 years after the light coagulation the girl was admitted to the Eye Department Ullevål Hospital After a long cross country skiing trip the eye had become red and she had noticed failing vision On admission there were signs of an uveitis with ciliary injection flare and cells in the anterior chamber The vitreous was so hazy that the eye ground could not be inspected The disc and the white scar above it could hardly be seen Ophthalmoscopy gave no suspicion of tumour growth and there was no shadow by trans scleral illumination The condition deteriorated during the following days and the cells in the anterior chamber took on an appearance of a more clotted fluffy material The tension rose considerably probably caused by a blocking of the trabecular meshwork by the exudate which gonioscopically was seen to cover the meshwork around the whole circumference

A puncture of the anterior chamber was made and a smear prepared which was

fixed and stained according to the Papanicolaou method and studied in the Depart ment of Pathology The finding of malignant cells was reported

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Fig 2

The enucleated left eye cut horizontally below the optic nerve and limbus 1 1



Fig 3
Retina above the papilla with atrophy gliosis and serous exudation Haematoxylin and *eosin* × *135*

lirly thickened especially on the nasal side all the way from the *ora serrata* to the papilla of the optic nerve (Fig 2)

Horizontal sections from different levels were studied after staining with haematoxylin and eosin

Sections above the papilla showed no tumour but an atrophic retina with gliosis and exudative changes was seen (Fig 3)

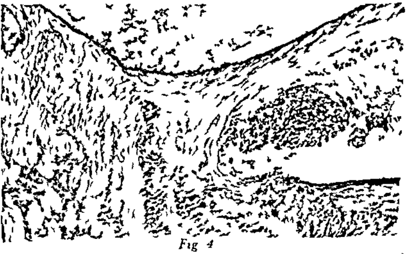


Fig 4
Retinoblastoma at the edge of the optic papilla Haematoxylin and eosin × 105



Fig 5
Retinoblastoma in the retina and subretinal space Haematoxylin and eosin × 105

Sections through the papilla demonstrated partial atrophy of the retina especially on the temporal side Between the layer of rods and cones and the pigment epithelium islands of tumour tissue were seen from the *ora serrata* to the edge of the papilla on both sides (Fig 4)

Below the papilla there was diffuse or focal growth of retinoblastoma in the retina and in the subretinal space (Fig 5)



Fig 6
Clusters of retinoblastoma cells in the anterior chamber Haematoxylin and eosin.
× 105

In all levels studied freely floating clusters of tumour cells appeared in the posterior and anterior chamber (Fig 6) partly attached to the surface of the iris cornea or trabecular meshwork

The tumour was poorly differentiated with only few rosette like structures many mitoses and large areas of necrosis with many neutrophile granulocytes The vitreous was protein rich and contained a limited number of erythrocytes and leucocytes

The lens was cataractous

Discussion

In this case the effect of the ^{60}Co applicator was convincing following two series of rather extensive deep X ray treatment which had failed to eradicate the tumour The degenerative changes which developed in the eye ground after several years indicate that X-ray treatment should be kept at a minimum

At the late recurrence the inflammatory signs dominated the clinical picture This has recently been discussed by Richards (1968) and Stafford Yanoff & Parnell (1969) Among 618 histologically verified cases of retinoblastoma the latter authors found that 6 6 % were primarily misdiagnosed as inflammatory conditions By histopathologic examination of 81 retinoblastoma eyes Jensen (1965) found inflammatory changes in 23

A recurrence of retinoblastoma as late as 12 years after the last irradiation treatment *is most unusual Paterson & Charteris (1965) report* a case with re currence 9 years after treatment with radon seeds Reese (1963 p 146) had seen three cases with recurrence several years after X ray treatment In the first of these cases the remaining eye was enucleated because of glaucoma 9 years after treatment for bilateral retinoblastoma After another 5 years the tumour had spread to the nose and paranasal sinuses The two other patients showed extraocular tumour growth 6 and 8 years after treatment

Activation of retinoblastoma many years after apparently successful radio logical treatment may be explained by some of the tumour cells having re mained in a state of suspended viability perhaps caused by the irradiation as indicated by a case reported by Calhoun & Reese (1942) They obtained an eye for histopathologic study *which had been treated 8 years previously* for retinoblastoma and where clinical follow up had indicated arrested growth On microscopic examination the eye contained tumour cells which did not look necrotic but had apparently lost their power to proliferate Another pos sible explanation is that these cases of late recurrence represent a new growth of tumour

The multifocal nature of retinoblastoma is well known and there are several

reports of tumour in the second eye appearing many years after treatment of the first eye e g 8½ years (Stallard 1962) and 12½ years (Skeggs & Williams 1966) The histopathologic study of the present case could give no clue to this problem except for the fact that a large area of the retina showed atrophy and gliosis without any trace of tumour tissue probably resulting from the irradiation performed many years previously whereas active tumour growth took place rather diffusely outside this field

This case represents our first and only experience regarding the value of exfoliative cytology in the diagnosis of retinoblastoma or rather in the differentiation between a neoplastic and an inflammatory condition within the eye

The cytologic diagnosis of material aspirated from the anterior chamber of the eye has been discussed by several authors (Verrey 1954 Ashton 1958 Schofield 1960 Naib Clepper & Elliott 1967 Richards 1968) Naib et al (1967) seem to have the most extensive experience in the cytologic diagnosis of retinoblastoma in aqueous aspirate They give a clear description of the characteristic findings which correspond closely to our own observations The importance of this method in the examination of eyes demonstrating clinical signs of inflammation with hypopyon or pseudohypopyon is stressed by Schofield (1960) and Richards (1968)

The finding of neutrophile granulocytes in the aspirate as in our case does not disfavour the diagnosis of a primary neoplastic condition especially when the latter is prone to undergo necrosis such as a retinoblastoma The finding of granulocytes in a sterile aspirate rather favours the diagnosis of neoplasia

Retinoblastoma cells in the aqueous can show some resemblance to lymphocytes If the cells are reasonably well preserved the chromatin structure of the nuclei is fairly characteristic and differentiation from lymphocytes should be easy

Addendum

March 197? almost 3 years after the enucleation of the last eye there are no signs of metastasis

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CORNEAL INDENTATION PULSE REDUCTION IN PREGNANCY

BY

IVAR HØRVEN and HALVARD GJØNNÆSS

A marked and highly significant reduction was observed in the pulse synchronous change in intraocular pressure in normal pregnancy as recorded by dynamic tonometry The decrease in corneal indentation pulse amplitudes most probably reflects a change in the peripheral vascu lar resistance It is suggested as a new and characteristic sign of preg nancy In addition a minor decrease of the intraocular pressure was found with no concomitant change in ocular rigidity

Key words applanation tonometry – corneal indentation pulse – dynamic tonometry – intraocular pressure – ocular blood supply – ocular pulsation – ocular rigidity – pregnancy – pulse rate

The corneal indentation pulse (CIP) amplitudes may be recorded in detail by dynamic tonometry (Hørven 1968) These amplitudes reflect the pulse syn chronous variations in intraocular pressure which are mainly dependent upon the excess of blood which enters the eye during systole causing a systolic dilata tion of the intraocular vascular bed As the choroidal circulation is con siderably larger than the retinal circulation dynamic tonometry reflects pri marily the situation of the choroidal vascular bed (Hørven 1970c)

The purpose of the present study is to introduce normal human pregnancy as a condition with significant reductions of the CIP amplitudes

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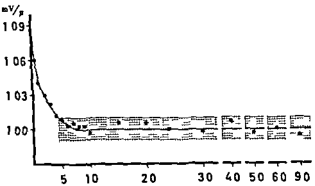


Fig 1

Dynamic tonometer output in mV per micron plunger movement during and after warm up period Shaded area = ± 1 % variation in sensitivity

Dynamic tonometry

The dynamic tonometer (Hørven 1968) is an improved stanardized electronic Schiotz tonometer which records eye tension and CIP amplitudes at all tension levels The dynamic tonometer output is 1 mV (±1 %) per micron of plunger movement (Fig 1) The output is linear and one scale reading Schiotz equals 50 microns of plunger deflection (Fig 2) A recorder sensitivity of 20 mV per paper division and a paper speed of 1 mm per second were used for the eye tension recordings (Fig 2) while a sensitivity of 2 mV per paper division and a paper speed of 5 mm per second were used for CIP amplitude registrations (Fig 3)

The CIP amplitudes were converted into mm³ change in intraocular volume

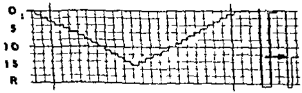


Fig 2

Calibration and linearity of the dynamic tonometer tested by use of a micrometer Recorder sensitivity is 20 mV per paper division. Each step of the curve corresponds to a 50 microns plunger displacement i e one scale reading Schiøtz (R) Arrow = tracing at scale reading 19 6 obtained by use of a calibration control test block.

Material

All subjects examined had healthy eyes Women with refractive errors less than 3 diopters were included

Non pregnant women

25 healthy females (nurses relatives etc) with an average age of 25 2 years (18–43) were examined The average blood pressure was systolic 118 2 mmHg (105–140) and diastolic 74 7 mmHg (70–80) All consecutive cases examined in the period July through December 1971 are included

Pregnant women

25 females were examined between 38–40 weeks of uncomplicated pregnancy The average age was 27 5 years (17–42) and the blood pressure was systolic 118 3 mmHg (100–140) and diastolic 78 8 mmHg (60–90) All consecutive cases examined in the period November 1970 through February 1972 are included

Methods

The examinations were performed in the following order (right eye – left eye) applanation tonometry eye tension recordings with *5 5 g – 10 g – 5 5 g plunger* weights corneal indentation pulse (CIP) amplitude registration The results were calculated separately for each eye whereafter the average value for the two eyes was calculated and used for the statistical evaluations

Brachial blood pressure recording was performed with a sphygmomanometer The difference between systolic and diastolic blood pressure i e the pulse pressure was calculated for each subject

Applanation tonometry

Following topical anaesthesia with 0 4 % oxibuprocain the applanation tonometry readings were obtained by use of a Goldmann applanation tonometer with the patient in the sitting position Applanation tonometry was omitted in a few cases

Fig 1 demonstrates that a warm up period of 5 minutes is necessary to give a dynamic tonometer output of 1 0 mV±1 % per micron of plunger movement. If a warm up period of ½-1 minute is used the output is about 1 05 mV per micron of plunger displacement Thus a CIP amplitude of 20 microns will be recorded with a 20 1 05 mV = 21 mV tracing a rather negligible numerical difference A proper warm up period is therefore not mandatory for CIP amplitude registrations

The need for a proper warm up period is pressing however when the eye tension is recorded especially when the 10 g plunger weight is used Example scale reading 15 (Schiøtz) equals 750 microns of plunger movement from the zero test block level Following a warm up period of ½-1 minute, 750 microns equals 750 1 05 mV = 787.5 mV If this tracing of 787 5 mV is calculated into microns of plunger deflection at the usual 1 mV = 1 micron basis a Schiøtz scale reading of 15 75 is obtained instead of the correct value of 15 This will seriously affect the ocular rigidity calculations To avoid error from minor fluctuations in output examinations with the dynamic tonometer are always begun by placing the tonometer head on the zero test block and then on a test block giving 630 microns of plunger deflection beyond the zero level corresponding to a 12 6 scale reading Schiøtz (Fig 2)

Results

The results obtained are summarized in Table I

Intraocular pressure

A good agreement was found between the Schiøtz and the applanation values Thus the non pregnant women showed average values of 13 8 mmHg (8–17 7) and 13 9 mmHg (11–17 25) respectively In the pregnant women the average values were 11 0 mmHg (5 9–14 3) and 11 0 mmHg (8–14 25) respectively The difference in intraocular pressure between non pregnant and pregnant women was significant at the 0 1 % level Eight of the pregnant women revealed Schiøtz and/or applanation readings below 10 mmHg This was seen only once in the non pregnant series

The ocular rigidity was of the same order of magnitude in the two groups The two methods gave similar results

The pulse rate averaged 70 5 beats per minute in the non pregnant and 88 3 beats per minute in the pregnant women This difference was significant at the 0 1 % level

Pulse pressure No difference was found in pulse pressure between the two series

The CIP amplitudes averaged 31 3 microns (17.5–50) in the non pregnant group A typical example is presented in Fig 3 In pregnancy the average CIP amplitude of 10 8 microns (5–21.5) was below the normal range ($P < 0\,001$)

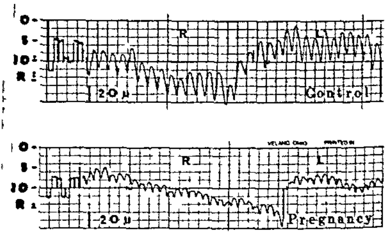


Fig 3
Corneal indentation pulse (CIP) amplitudes in a non pregnant woman (above) and during normal pregnancy (below) Recorder sensitivity is 20 mV (eye tension) and 2 mV (CIP amplitude registration) per paper division and the corresponding paper speed is 1 mm and 5 mm per second respectively

(ΔV) by the use of converting tables based upon Langham s and Hetland Eriksen s data as previously described (Horven 1970a) When multiplied with the exact pulse rate the ΔV per minute was revealed The P_o (Schiotz) value was based upon the two 5 5 g recordings Occasionally the difference between them exceeded half a scale reading In such cases the average value was used P_o P_t and V_c were calculated by use of Friedenwald s 1955 converting tables (Friedenwald 1957)

Ocular rigidity was calculated in all but a few cases by use of the differential Schiotz method (5 5 g and 10 g plunger weights) In most cases the ocular rigidity was also calculated from the 10 g Schiotz and the applanation results according to Ytteborg (1960)

$$K = \frac{\log P_{t10} - \log (\text{Applanation} + 1)}{V_{c10} - 0\,44}$$

In this formula 1 mmHg is added to the applanation value to compensate for the applanation tonometry being performed on sitting subjects 0 44 mm³ is the V_c value obtained by applanation tonometry (Goldmann & Schmidt 1957) This formula gives about 5 % lower K values than those obtained by the more commonly used formula

$$K = \frac{\log P_{t10} - \log \text{Applanation}}{V_{c10}}$$

(Fig 3) This finding was fairly constant only two pregnant women showed CIP amplitudes above 17 microns while all the non pregnant women demonstrated CIP amplitudes above this level

The ΔV averaged 207 6 mm³ per minute (127 5–340.5) in the non pregnant and 85 9 mm³ per minute (44–145) in the pregnant women This difference is also highly significant ($P < 0\,001$)

Discussion

The present study brings to attention a marked reduction in CIP amplitudes as a sign of pregnancy The mechanism of this reduction in CIP amplitudes is unknown Methodological errors are unlikely as the control material of non pregnant women showed normal amplitudes identical to those previously reported from subjects in the same age and sex groups (Hørven 1970b)

Theoretically the findings may be explained in several ways

1 Alterations in intraocular pressure have been shown to imply changes in CIP amplitudes most pronounced at elevated intraocular pressure levels (Hørven 1970b) A change in the intraocular pressure as seen in the present study provokes a less than 10 % change in CIP amplitudes (Bynke 1969 Best 1971)

2 Decreased ocular rigidity implies reduced CIP amplitudes (Syrdalen 1970) It is well known that a change in elasticity of ligaments and connective tissue occurs in pregnancy A corresponding change might occur in the ocular elasticity i e in the ocular rigidity In the present series however no such change was observed

3 Increased pulse rate implies reduction of the CIP amplitudes The ΔV per minute however is either unchanged as seen in atropin induced tachycardia (Hørven et al 1971a) or increased as seen during exercise (Hørven 1971) The moderate increase in pulse rate observed in the pregnant women can explain only a minor part of the decrease in CIP amplitudes as the reduction in the ΔV per minute was quite large This is a somewhat conflicting finding because in pregnancy increased pulse pressure is the rule along with increased cardiac output and a slight increase in pulse rate (Mendelson 1965 MacGillivray 1970) These changes are however compensated for by the baroreceptors In fact they are overcompensated as the blood pressure is known to decrease during pregnancy A disproportionate fall in the diastolic level sometimes produces capillary pulse (Mendelson 1965) In the present series no significant difference between the two groups was found in either blood pressure or pulse pressure

Table 1

Statistical evaluation of results (Student s t test)

	Non pregnant women			Pregnant women			t value	Significance level
	N	Mean	SD	N	Mean	SD		
Age	25	25 2	7 15	25	27 5	5 94	1 237	not sign
I O P (mmHg – Schiøtz)	25	13 8	2 43	25	11 0	2 22	4 254	P < 0 001
I O P (mmHg – Appl)	18	13 9	1 85	23	11 0	1 79	5 053	P < 0 001
k value (5 5 g/10 g)	25	0 0175	0 0045	24	0 0185	0 0034	0 880	not sign
k value (Appl /10 g)	17	0 0191	0 0030	23	0 0192	0 0026	0 110	not sign
Pulse rate	25	70 5	10 01	25	88 3	16 79	4 553	P < 0 001
Pulse pressure	25	43 5	7 57	25	39 5	7 71	1 851	*not sign*
CIP amplitude (microns)	25	31 3	9 44	25	10 8	4 58	9 769	P < 0 001
1V (mm^3 per minute)	25	207 6	51 51	25	85 9	27 08	10 456	P < 0 001

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4 A decrease in ocular blood supply provokes a corresponding decrease in CIP amplitudes (Nornes et al 1971a) and ophthamic artery pressure (Hollenhorst 1959) Vancea (1930) noted reduction of ophthalmic artery pressure in 76 % (38/50) of pregnant women More recent reports demonstrate the ophthalmic artery pressure during pregnancy to be normal (Omarov & Mamedov 1971) or slightly elevated (Leonardi 1956) Accordingly it seems rather unlikely that decreased ocular blood supply exists during pregnancy as a matter of importance in this respect

5 A shift towards non pulsatile intraocular blood flow may theoretically give low CIP amplitudes without reducing the ocular blood supply At present no convenient method is available for evaluation of this possibility Zero or close to zero CIP amplitudes have been recorded in eyes with full vision (Horven 1970c, Syrdalen & Horven 1970) Theoretically two possibilities exist for explanation of this situation the amount of blood entering the eye per time unit may be identical in systole and diastole This would imply a definite non pulsatile blood flow pattern Or corresponding to the extra amount of blood entering the eye per time unit in systole a similar extra amount may leave the eye simultaneously thus abolishing the systolic increase in the intraocular blood volume This could be explained by a reduction of peripheral vascular resistance and would imply increased systolic ocular blood velocity In accord with this hypothesis the blood flow velocity has previously been postulated to be increased in pregnancy (Herbert et al 1958)

In pregnancy the venous blood pressure of the lower extremities rises progressively while in the upper extremities there is a tendency for a slight decrease (Mendelson 1965) These changes are due partly to hormonal influences on the vascular tone but mainly to mechanical causes The decrease of the venous blood pressure seen in the upper extremities therefore is probably accentuated in the head Besides the viscosity of the blood decreases corresponding to the well known decrease of haematokrit values seen in pregnancy These two factors would probably change the blood circulation in the direction of an easier escape from the eye

A decrease of the intraocular pressure during pregnancy was first noted by Imre (1922) and confirmed later by a number of authors (Marx 1923 Patat 1938 Dominguez 1951 Becker & Friedenwald 1953) and by the present study Most probably this decrease is explained by the corresponding reduction of venous pressure in the head and not by a hypothetical decrease of the ocular blood supply (Bynke 1966 Nornes et al 1971b)

It may well be that hormonal changes triggered by the pregnancy induce the low CIP amplitudes through action on peripheral blood vessels Further work on this subject is in progress

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TREATMENT OF CORNEAL ULCERS WITH CYSTEINE

BY

ULF KRAUSE and KAISU NEVASAARI

Consequent to reports of demonstrable collagenolytic activity in connec tion with several types of corneal ulcer some twenty patients were treated with cysteine chloride wh ch is known to inhibit this collagenolytic ac tivity The drug was administered as 0 1 M eye drops four times a day In three patients the effect was very good and in two it was considered favourable In the other cases the evaluation of the results was hampered chiefly by pathological conditions concomitant with tl e corneal affection. The only side effect noted from the drug was smarting Since it appears to entail no risks cysteine therapy may be considered worth trying if favourable results cannot be obtained by other *medication*

Key words cysteine – corneal ulcer – treatment – side *effect* – *collageno lytic* activ ty

Collagenolytic activity has been demonstrated on the cornea in connection with pathologic processes both in rabbits (Slansky Freeman & Itoi 1968 Itoi et al 1969 Gnadiger et al 1969 McCullen et al 1969 Pfister et al 1971) and in human subjects (Slansky et al 1969 Brown Akiya & Weller 1969 Brown & Weller 1970) Collagenolytic effect can be counteracted by inhibitors such as cysteine penicillamine or ethylene diamino tetra acetic acid (EDTA) salts The effects of cysteine and EDTA on the cornea have been studied by Slansky et al (1969 1970) Itoi et al (1969) Brown Akiya & Weller (1969) and Brown

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& Weller (1970) According to Brown & Weller (1970), the most efficient inhibitor proved to be cysteine whereas the calcium salt of EDTA had no effect Itoi (1969) claimed however that it had an inhibitory effect Seifter & Gallop (1962) reported that calcium improved collagenase activity Takahashi & Seifter (1970) have assumed that calcium is indispensable for the stabilization of the active collagenase molecule

In the literature we have found the use of cysteine mentioned in connection with alkaline injuries some herpetic and marginal furrow ulcers and with ulcers of recent corneal transplants (Brown & Weller 1970 Brown & Hook 1971) The assumption has been advanced, however that cysteine may be effective in treating many types of corneal affections (Brown Akiya & Weller 1969 Brown & Weller 1970)

Material and Methods

In our hospital we have treated with 0 1 M cysteine chloride solution some 90 patients who had corneal ulcerations due to causes other than alkaline injuries Drops were administered four times a day At first this treatment was considered a last desperate resort but later it was used for much less serious indications Selections from our observations are recapitulated below

CASE REPORTS

Case 1

A man of 79 had undergone a cataract operation six months previously Postoperatively the cornea revealed superficial punctate keratitis which had been treated with sulpha ointments Gradually the cornea was vascularized except for the middle parts which on admission to hospital showed a deep crater like ulceration The bacterial culture taken was spoiled and the possible bacterial background of the disease is therefore not known The ulcer was treated without result for 17 days with topical antibiotic and sulpha medication The patient was then prescribed 0 1 M cysteine chloride solution four times a day under the protection of Polysporin® (Burroughs Wellcome & Co London) instillation The next day the ulcer had a better appearance four days later it was already very small and after 8 days of treatment the wound had closed The pathologic process has not recurred

Case 2

A boy of 13 had undergone penetrating keratoplasty for keratoconus 4 months previously Postoperatively he was continuously on topical cortisone antibiotic drops At a routine examination a superficial ulcer surrounded by grayish infiltrate was noted in the graft of the subjectively symptom free eye

The bacterial culture grew *Staphylococcus albus* The first treatment prescribed con sisted of chloramphenicol drops later followed by sulpha and mycostatis combined with systemic administration of 250 mg Tetracycline four times a day The corneal process continued to expand for which reason cysteine therapy was started after a week with 1 drop four times a day In addition the treatment consisted of 5 mg Prednisone three times daily Two days after the institution of therapy there was dis tinctly less ulceration, and after 9 days it had completely closed The affection has not recurred within 9 months

Case 3

A man of 70 had absolute glaucoma in his left eye On admission the eye revealed an extensive central ulcus serpens and hypopyon. The bacterial culture was negative. Local chloramphenicol therapy gave no favourable effect within three days and enucleation was under consideration However the treatment was then modified by addition of a cysteine instillation four times a day Four days later the wound was distinctly better and 12 days after the institution of cysteine therapy the corneal ulcer had healed completely and hypopyon had disappeared The cornea showed a bullous keratopathy which has remained unchanged for more than 6 months

Two further patients with recurrent corneal ulcer were treated with cy steine The effect of the drug was considered favourable One case of keratitis disciformis failed to show any response whatever to crysteine

In addition to these cases more than ten other corneal ulcers were treated with cysteine drops The complexity of the pathologic conditions for instance a concomitant conjunctivitis vernalis or severe hypoproteinemia is the reason why it has not been possible to evaluate the effectiveness of cysteine medica tion Objectively cysteine therapy does not seem harmful One patient com plained of smarting caused by the drops for which reason cysteine had to be replaced by another drug

Discussion

Collagenolytic activity has been demonstrated in the human cornea in con nection with alkaline injury and certain active pathologic processes (Slansky et al 1969 Brown Akiya & Weller 1969) Theoretically the use of collagenase inhibitors such as cysteine should be beneficial in these situations and animal experiments seem to show that this is in fact the case Few reports are found in the literature concerning results obtained in human subjects (Brown & Wel ler 19 0 Brown & Hook 1971)

Cysteine and cysteine chloride are water soluble and oxidize in neutral or mildly alkaline solution into inactive cystine. With water cysteine chloride

forms an acid solution Copper and iron are efficient inactivators of cysteine If other topical agents containing copper or iron are used in connection with cysteine treatment cysteine may become inactivated Because of these factors for example the effect of cysteine therapy may be difficult to evaluate

Two patients (cases 1 and 2) in whom the cysteine therapy was found to produce good results were given the medication under the topical protection of Polysporin® This *preparation contains e g polymyxine sulphate* Sandberg (1964) has shown that polymyxine given preoperatively accelerates wound healing in the rat and stimulates collagen formation of the scar tissue

Encouraging and in some instances quite good results were achieved with 0 1 M cysteine instillation in a few cases of corneal ulcer Since this drug seems to have no objectively observable side effects and it also seems to be well tolerated it appears justifiable to recommend it for more extensive use even though no evidence of its beneficial action in the light of large materials is yet available

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CONTRALATERAL RHINOSTOMY FOR DACRYOCYSTITIS DUE TO FACIAL MALFORMATION

BY

IMRE KORCHMÁROS

In a case of *sinistral* dacryocystitis due to congenital facial malformation the rhinostomy was performed through the nasal bone and the nasal septum into the *dextral* nasal cavity because of the atresia of the sinistral nasal cavity.

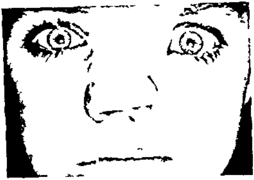
Key words: dacryocystitis – congenital facial malformation – contralateral rhinostomy – operation – atretic nasal cavity.

Because of the congenital facial malformation of a 14 year old boy (Fig. 1) his sinistral lacrimal duct became osteally atretic. This fact resulted in dacryocystitis.

Rhinology and roentgenogram: on the left side the nostril is atretic, the nasal cavity is fissure like and the frontal sinus is underdeveloped.

The restorative operation for the lacrimal passage was performed on June 3rd 1969 under block anaesthesia. The lacrimal sack was found to be crumpled and have walls of uneven thickness. The removed osseous flap was loosely connected to the dislocated nasal septum, while according to the syringing test the narrow and atretic nasal cavity proved to be inappropriate for the drainage of the tears. Therefore instead of extirpating the lacrimal sac

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Fi, 1
The patient with congenital facial malformation

we performed a contralateral rhinostomy A window was drilled into the nasal eptum and the rhinostomy was performed by making use of the mucosa on the dextral side of the nasal septum

Dacryocystitis and epiphora were eliminated Control period 25 months

The post operative situation was recorded by a roentgenogram after intro ducing a cannula probe into the new lacrimal passage (Fig 2)



Fi >
R entgen gram after the c ntralateral rh nostomy The cannula is introduced into the new la rimal pas a e formed through a nasal bone and a nasal septum window

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THE ULTRASTRUCTURE OF THE EXTRACELLULAR COMPONENTS OF THE LIMBAL CONJUNCTIVA IN THE HUMAN EYE

BY

AMUND RINGVOLD

The limbal conjunctiva (i e a 2–3 mm broad zone of connective tissue around the cornea) from five human eyes was studied It has been shown that the bulk of extracellular material in this part of conjunctiva is made up of collagen fibrils that mostly were arranged parallel to the surface of the sclera Additionally this loose connective tissue contained the following extracellular elements typical elastic fibers 1000 Å banded material banded subepithelial fibrils symmetrically cross banded fibrils finely fibrillar material dense sheet like structures and basement membranes Evidence is presented that the dense sheet like structures probably are formed by keratinization of the conjunctival epithelium

Key words conjunctiva – connective tissue – histology – human eye – ultrastructure

The conjunctiva is a connective tissue sheet covering both the anterior part of the sclera and the inner surface of the eyelids According to light microscopic studies (Kolmer & Lauber 1936 Rohen 1964) conjunctiva contains an abundance of collagen and elastic fibers and both of them appear in increasing amounts with increasing age Additionally numerous reticular fibers are present particularly in the subepithelial and in the perivascular area The presence of collagen and elastic fibers in the conjunctiva has been confirmed by electron microscopic studies both on conjunctival vessels (Tamura 1967 Hara & Hiwatari 1969) and on conjunctival tissue from the limbal region (Hogan et al 1971)

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The purpose of this investigation is to obtain further information on the extracellular components of the normal adult human conjunctiva. It was prompted by our interest in the extracellular components of conjunctiva in eyes with pseudo exfoliation syndrome (*Ringdom 1972*) and thus it also serves as a normal reference for our studies on this aspect.

Material and Methods

Five human eyes enucleated because of tumor of the posterior part of the bulbus were studied. No other abnormalities were found in any of these normotensive eyes. The patients were 28, 54, 58, 63 and 74 years old respectively at the time of operation.

Specimens from three bulbi were fixed for 1–2 hours in 2 % OsO_4 buffered to pH 7.4 with phosphate buffer. The remaining two specimens were fixed for 2 hours in 1 % OsO_4 buffered to pH 7.4 with 0.16 M sodium cacodylate buffer. Tissue blocks from one of the latter eyes were stained *en bloc* for 1 hour in 2 % uranyl acetate adjusted to pH 6.5 with sodium acetate buffer. Tissue blocks from all eyes were dehydrated in graded acetone solutions and embedded in Araldite. Sections were made with an LKB Ultrotome and stained with uranyl acetate followed by lead citrate. Siemens Elmiskop I and IA were used.

Results

The extracellular material of the conjunctiva is composed almost entirely of collagen fibrils showing the well known cross band pattern with an axial period of about 640 Å and their diameter measured between 200 Å and 1700 Å (Fig. 1). The fibrils appearing either singly or lying closely together in small bundles were loosely organized in a highly irregular arrangement. However most of the collagen fibrils had a course roughly parallel to the scleral surface. Typical elastic fibers also occurred in moderate amounts (Fig. 6) consisting largely of an amorphous material surrounded by a microfibrillar component as recently described by Ross & Bornstein (1970). The microfibrils measured about 100 Å in diameter and were partly embedded in the peripheral part of

Fig. 1

Subepithelial region of the limbal conjunctiva. Note the loose texture of this connective tissue. Epithelial cell (E). Collagen fibrils (cf). Subepithelial banded fibrils (sbf). Symmetrically cross banded fibril (sf). × 30 000


E
sbf
cf
sf

the amorphous material The conjunctival stroma showed a gradually increasing compactness towards the sclera This thin zone of connective tissue interposed between the conjunctiva and the sclera (i e Tenon s capsule and episclera) is not described in this study

In addition to the collagen and the elastic fibers small amounts of the following components were also found in the conjunctival stroma so called 1000 Å banded material banded subepithelial fibrils symmetrically cross banded fibrils finely fibrillar material, dense sheet like structures and basement membranes

The *1000 Å-banded material* (Fig 2) formed long fibers (up to 17 μ long and up to 0 6 μ thick) that had rather distinct and irregular outlines Along the single fiber alternating dark and light regions (300 Å and 800 Å in length respectively) were present bringing about a period length of about 1100 Å Usually no differences were revealed between peripheral and central material



Fig 2

1000 Å banded material adjacent to a fibroblast (F) In the central part of the lower structure (arrow) one additional dark cross line is present in the middle of light regions × 40 000

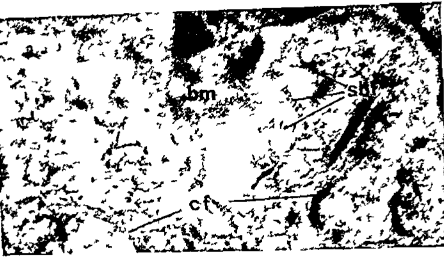


Fig 3

Subepithelial banded fibrils (sbf) connected with the epithelial basement membrane (bm) Epithelial cell (E) Collagen fibrils (cf) × 60 000

of the fiber However in a few cases obliquely sectioned bundles showed a less electron dense more or less homogeneous central core The 1000 Å banded material was absent in a 10 μ broad zone beneath the epithelium but otherwise it was found scattered throughout the limbal area

The *banded subepithelial fibrils* (Fig 3) appeared similar to the structure which originally was reported as unusually banded reticular filaments of normal human epidermis (Brody 1960) and which has been described extensively since then by several authors (Palade & Farquhar 1965 Rowlatt 1969 Bruns 1970 Briggaman et al 1971) The total length of these fibrils measured up to 0 5 μ they were 150–400 Å wide and several cross bands appeared along their course Such fibrils were encountered exclusively in the immediate sub epithelial zone where they in many instances had a course perpendicular to the epithelial basement membrane and their ends seemed embedded in the basement membrane itself The fibrils were curved and through numerous branches joining neighbouring fibrils they apparently formed a network beneath the epithelial surface of conjunctiva.

The *symmetrically cross banded fibrils* (Fig 4) were first described in the iris stroma (Ringvold 1970) They appeared as bundless of tightly packed fila ments and single bundles were up to 1 4 μ long and 1000 Å wide The period length measured about 650 Å and as shown in Fig 4 each period contains



Fig 4
Symmetrically cross banded fibril The cross band pattern is symmetrically spaced either about one cross line (single arrow) or about the midway between two dark lines (double arrow) $\times$ 100 000

cross lines arranged in a symmetrical pattern Some of the bundles spread out fan like at their ends whereby the filaments (about 50 Å thick) became particularly clear In other cases they ended relatively bluntly or even tapered off towards the ends Longitudinal clefts along parts of the bundles brought about a splintered appearance of some structures A very loose texture of several bundles joining each other also occurred The symmetrically cross banded fibrils were ubiquitously distributed in the limbal region but they were most frequently encountered in the superficial part of conjunctiva

The *finely fibrillar material* (Fig 5) consisted of numerous rather straight fibrils that showed an even thickness of about 200 Å Along some of them faint cross lines were seen Such fibrils frequently formed small groups and they were observed in all parts of the limbal conjunctiva

The conjunctival surface was not always formed by epithelial cells In those parts where an epithelial membrane was lacking the superficial zone was made up of a *dense sheet like structure* (Fig 6) These sheets were composed of differently shaped (straight or curved bands jagged forms) dense elements that were tangled more or less loosely together Often the dense material was so tightly packed that no substructure could be distinguished However regions of lower density in the peripheral part of dense elements revealed a network of filaments The sheet like structure showed numerous clefts in between the single dense elements and some of these openings contained cellular remnants mainly as membrane fragments ribosomes and damaged mitochondria (Fig 7) None of the above described extracellular components were found within such clefts It seems adequate to note that such superficial dense material was present in all specimens However it was not prominent in the eye from the 28 year old patient Even though it is beyond the scope of this study it should

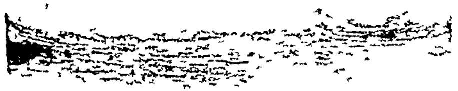


Fig 5
Finely fibrillar material consisting of numerous parallel fibrils showing faint cross lines × 30 000

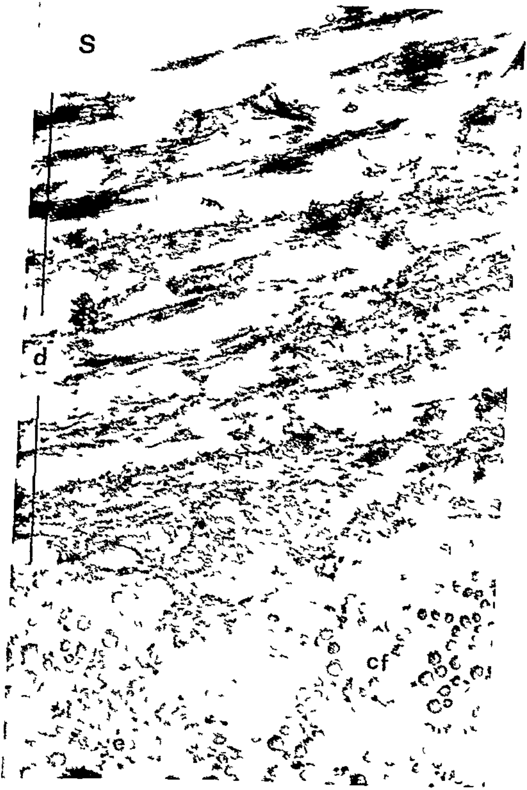


Fig 6

Dense sheet like structure (d) forming the superficial part of conjunctiva Surface (S) Cross sectioned collagen fibrils (cf) and elastic fiber (e) × 40 000

additionally be mentioned that sometimes apparently intact epithelial cells contained an abundance of parallel filaments

Basement membranes occurred in the vessel walls and beneath the epithelium In both regions it was formed by a dense zone separated from the adjacent cell layer by a light space of about 300 Å thickness Like most basement membranes the dense zone consisted of the well known finely granular material mixed with irregular filaments The endothelial basement membrane varied in thickness along the circumference (up to 0.5 μ wide) and in some



Fig [illegible]
Higher magnification of the superficial dense material enclosing damaged cells (C) and ribosomes (r) × 80 000

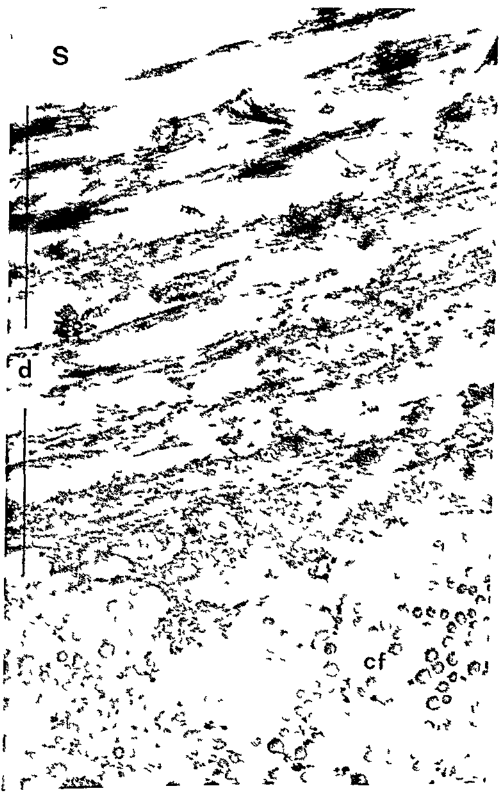


Fig 6

Dense sheet like structure (d) forming the superficial part of conjunctiva Surface (S) Cross sectioned collagen fibrils (cf) and elastic fiber (e) × 40 000

junctival epithelium (Hogan et al 1971) All these observations together with the fact that the dense superficial structure appeared similar to keratin material of the epidermis (Brody 1960 Hashimoto 1971) at the early stage of keratinization make it reasonable to assume that these sheets are of a keratin nature

It appears from the present study that the conjunctiva contains a great number of morphologically different components However it seems evident that more definitive work is necessary before specific morphologic characteristics of these elements can be correlated to their physiologic activity

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parts it was multilayered Contrary to this the epithelial basement membrane showed an even thickness of about 700 Å In both cases the values express the *distance between the cell membrane and the external border of the granular* material

Finally in a few sections some irregularly outlined patches and dense streaks of a partly granular partly flocculent substance were found scattered among the other connective tissue components

Discussion

Apart from the basement membranes and the typical collagen and elastic components little other than the morphological characteristics are known about the described extracellular elements of conjunctiva However from previous studies it is clear that the 1000 Å banded material is present both in intraocular and probably in extraocular connective tissue (*for references see* Vegge & Ringvold 1971) whereas the banded subepithelial fibrils have been found associated with basement membranes under stratified as well as simple epithelia (for references see Bruns 1970) It has been postulated that the fibrillar network formed by the latter type of fibril is anchoring the basement membrane of the stratified squamous epithelium which is exposed to considerable friction to the underlying connective tissue (Palade & Farquhar 1965) If this hypothesis is correct the occurrence of such fibrils in conjunctiva is perhaps not surprising since this tissue likewise is subject to some mechanical forces through the constant movement of the eye

The symmetrically cross banded fibril has previously been observed in the iris stroma (Ringvold 1970) and in the trabecular meshwork (Vegge & Ringvold 1971) but has apparently not yet been demonstrated outside the sclera except in the present study The morphology of these fibrils resembles some twisted types of collagen fibrils present in amyloid tissue (Merker et al 1966) and in the dermis of patients with pseudoxanthoma elasticum (Danielsen et al 1970) However they differ from these as well as from native collagen fibrils by their symmetrical arrangement of cross bands

The dense sheet like structure which was observed only in regions where the conjunctival epithelium was absent always showed a superficial position and it enclosed some cellular remnants On the other hand connective tissue components were not demonstrated within such sheets Furthermore sometimes intact epithelial cells contained an abundance of parallel filaments probably identical with the recently described cytoplasmic tonofilaments of the con

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FLICKER ELECTRORETINOGRAPHY

BY

N. I. BACHEN and M. DAVANGER

Flicker ERGs from normal human eyes are recorded using an averaging technique. After 300 msec the curve is in a stationary phase with strict periodicity. It is constructed by algebraic summation of individual flash responses with 'head-to-tail' overlapping in higher frequencies. At a flash frequency of 25 cps the a-wave is placed at the negative deflection following the b-wave of the foregoing flash, and the period becomes simple diphasic sinusoid. Further increase of the frequency causes the amplitudes of the sinusoid curve to gradually decrease. In 12 out of 17 cases an ERG periodicity was present at a flicker frequency of 100 cps. In 3 cases the ERG periodicity was 50 cps even at a flash frequency of 100 cps, indicating an ERG response to only every second flash. At frequencies 40 cps and higher an off-response is present at the termination of the flash train. This off-response is increasingly impressive with increasing frequencies because of the reduction of the amplitudes of the foregoing waves.

Key words: electroretinography – flicker – off-response – oscillatory potentials

The electroretinogram evoked by continuous light or by a single flash is dominated by the response of the 125 million rods of the human retina, and the function of its 4–7 million cones thus cannot be well evaluated by this method. This has been considered a serious handicap for both clinical and experimental work. Riggs (1958) summarized the means that may be employed to uncover the photopic cone response. The use of red light, light-adapted eye, flashes of

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constant duration usually approximately 700 msec The flash intensity was set to scale reading 4 The photostimulator was centered at a distance of 30 cm from the eye

A Lovac ERG contact lens (Medical Workshop Holland) with a refractive power of +100 D and a corneal (active) electrode and a conjunctival (re ference) electrode was used The test subject s forehead was grounded and the laboratory was electrically shielded

The ERG signal was amplified by a DISA amplifier with a frequency range of 2 to 10 000 cps (at 3 dB) and an input impedance of 200 megaohm shunted with 30 pF (balanced) 100 regaohm shunted with 60 pF (single ended)

To improve the signal noise ratio an averaging technique was applied using a CAT 400C Each curve presented is the average curve of 50 ERG samples obtained by repetitive presentation at regular intervals (about 1 5 sec) of the flash or the flash train The average curve was recorded from the computer memory by an X-Y plotter

The material consists of 17 individuals all with normal eyes One eye from each subject was tested The pupil was dilated with cyclopentolate 1 % The test subject was placed in a recumbent position The experiments were per formed in average artificial room lighting to which the subject had adapted

The individuals were subjected to an experimental program starting with the 50 single flashes followed by the flicker trains with increasing flicker frequen cies as seen in Fig 2 In some cases additional experiments were performed as seen from the Figures

Results and Discussion

The flicker ERG as constructed by algebraic summation of individual flash responses

Each flash in a regularly spaced flicker flash train evokes an electroretino graphic response which is influenced by the flash interval and by the position of the flash in the flash train.

The influence of the flash interval is demonstrated in Fig 1 which shows ERGs evoked by a flash train consisting of only 2 flashes In the upper curve the flash interval τ is long 1 010 msec in which case the same response is evoked by both flashes Curve No 2 is evoked by 2 flashes with a flash interval of 40 msec The effect of the second flash may be obtained by subtracting a single flash ERG (curve No 3) from the double flash ERG This subtraction yields a result (curve No 4) which may be considered as consisting mainly of an a wave (consistent with the finding of Francois G de Rouck (1962)) and which is quite different from the response evoked by flash No 2 in the first curve

short duration the study of the off response rather than the on response. As he points out it is possible to combine the features of several of these effects by using prolonged stimulation with flickering light.

By low frequent regular flicker each flash evokes a response which is seen in the ERG. As the flicker frequency is increased a frequency is arrived at in which a periodicity can no longer be discerned in the ERG. This frequency is the ERG flicker fusion frequency at the given experimental conditions.

It has been shown that relatively low ERG flicker fusion frequencies are obtained from animal eyes dominated by rods (e. g. guinea pigs 30–40 cycles per second (cps)) by comparison with eyes dominated by cones (e. g. cat 60–70 cps and pigeon 150 cps (Granit 1958)). Dodt & Wadensten (1954) found ERG flicker fusion in normal human eyes around 70 cps and in patients with primary total colour blindness around 20–25 cps. It is concluded from these and similar findings that cones are capable of following faster flickers than are rods (Granit 1958).

In eyes with both rods and cones such as the human eye higher rates of flicker (above 20–30 cps) seem to yield less activity from the rods and thus bring out cone activity (Riggs 1958). On this basis the use of flicker stimuli for ERG has been recommended for clinical use to obtain information on the *function of the photopic cone system of the human eye* (Granit 1958).

On this background a set-up has been developed in our laboratory for the registration of flicker ERG from a human clinical material. Our arrangement seems to yield accurate and reproducible results also in high frequent flicker up to about 100 cps. As a basis for the use of this method in clinical work flicker ERG has been recorded in a normal material. The experimental conditions differ on some points from those reported by earlier investigators. The flicker stimuli consisted of regularly spaced flashes of very short duration. The regular flicker trains lasted sufficiently long to reach the stationary phase of the ERG response. The off response evoked by the termination of the flicker train has been recorded. An averaging technique by the use of a CAT computer was employed.

Our experiments have brought some observations which may be of interest. These observations will be presented and discussed.

Methods and Material

A Grass photostimulator (PS 1) delivering flashes lasting about 10 μsec was driven externally by a pulse generator. It produced single flashes or flash trains with a preselected frequency up to 100 cps. The flash trains had a

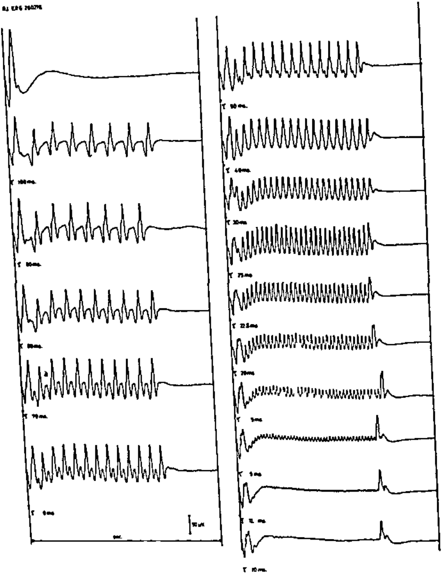


Fig 9
Single flash ERG and regular flicker flash ERGs at increasing frequencies The flashes are indicated by dots Flash interval τ is indicated

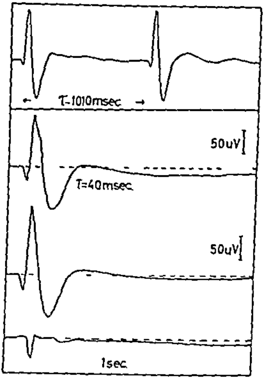


Fig 1

The influence of the flash interval on the effect of the second flash in double flashes The last curve indicating the effect of the second flash at a flash interval τ = 40 msec is calculated by subtracting a single flash ERG from a double flash ERG

The influence of the position of the flash in the flash train on the response to this individual flash is seen in Fig 2 In higher flicker frequencies the curve is dominated by the response to the first flash during the first $^1/_3$ sec which is about the duration of a single flash ERG The responses to the flashes following the first are superimposed on this first response and are not always clearly discernible During this phase the regular cycles of the flicker stimulus do not result in regular periodicity of the response But gradually after about $^1/_3$ sec the curve arrives at a *stationary phase* in which strict and regular periodicity is attained In the stationary phase the response pattern consists of repetitive identical periodic responses in which a waves and b waves can be clearly identified at the lower flash frequencies

The response pattern is usually rather uniform and more or less similar to the pattern reproduced in Fig 2 in most cases However in some individuals the curves may show other details as is demonstrated in Fig 3 In this case the a wave is double in the single flash ERG and oscillatory potentials are present

b wave of the foregoing period and the period becomes simpler diphasic sinusoid This simple pattern is also seen at higher frequencies but the amplitudes are gradually decreasing with increasing frequencies

Evidently a main cause of this decrease of amplitudes must be a head to tail overlapping of the individual flash evoked responses which are telescoped into each other By algebraic summation of b waves and a waves the resulting amplitudes must be reduced

In addition to this process of interference between individual flash responses the flicker ERG is presumably also influenced by a gradual change of the individual flash response with increasing flicker frequencies But because of the overlapping this change of the individual flash response is not seen directly from the curves

This leads to the problem of isolating the individual flash response at the different frequencies that is to calculate the contribution of each single flash in the flash train to the flicker FRG in its stationary phase

The response evoked by the *last* flash in a long flicker train may be isolated by the following method The stationary phase including the termination of the flicker FRG evoked by N flashes is recorded Thereafter a similar ERG evoked by N 1 flashes is recorded Now the contribution of the last flash No N may be obtained by subtracting the second curve from the first This subtraction may be performed by a graphical procedure or the result may be obtained more directly by the subtraction being performed by the CAT computer

It will be understood that actually it is not necessary to record the second curve with N 1 flashes As the flicker ERG is supposed to be in its stationary phase this curve may be obtained by shifting the first curve *one period to the* left (Fig 4)

This method will bring out the individual flash response of the stationary phase only if the electroretinographic effect of the last flash is identical with the effect of the foregoing flashes But this may not be the case for high frequency flicker *because* of the off response evoked by the termination of the *flicker train* as such as will be demonstrated and discussed later

Because of the latency time of the ERG there will be a phase shift between the flash train periodicity and the response periodicity This phase shift may be observed in the curves at the termination of the train

The ERG flicker fusion frequency Alternating ERG responses

In 17 of the 17 flicker ERGs presented in this material a well preserved periodicity was apparent even at a flash frequency of 100 *cps* which was the highest frequency obtainable with our photostimulator (Figs 5 6 8 9 and 10)

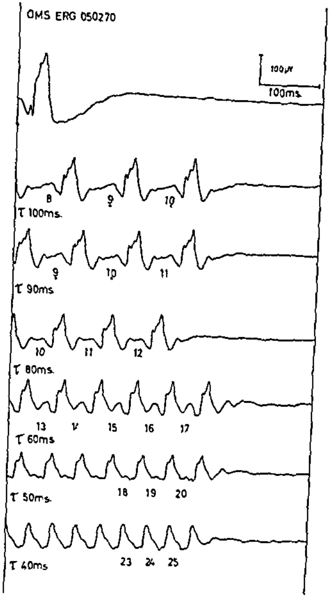


Fig 3
Oscillatory potentials in flicker ERG gradually disappearing at *increasing frequencies*

at the ascending branch of the b wave both in the single flash ERG and in the low frequency flicker curves By increasing frequencies the oscillatory potentials gradually disappear one by one

At lower frequencies the period is polyphasic and *quite complex* *This comes* to an end at a flash frequency of about 25 cps i e flash interval $\tau = 40$ msec At this frequency the a wave is placed at the negative deflection following the

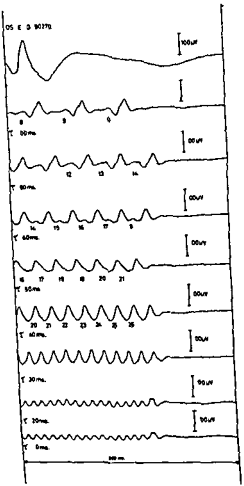


Fig 5
Flicker ERGs at increasing flicker frequencies 50 cps response pattern at a flicker frequency of 100 cps (τ = 10 msec)

other elements being in a relative refractory phase In some cases this may lead to coupling of responses to every second flash

The ERG off response evoked by the termination of a high-frequent flicker train

The termination of a low frequent flicker train up to 33 cps does not evoke

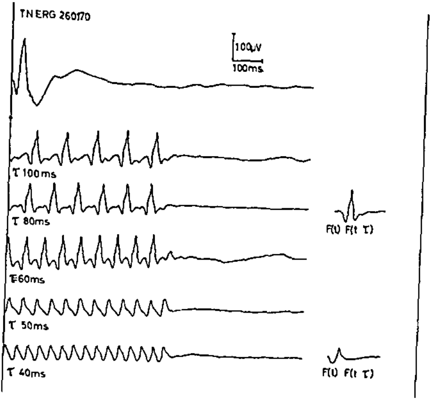


Fig 4
Calculation of the individual flash response in flicker ERG

The flicker ERG of the remaining 5 subjects was flat i e aperiodic in the stationary phase at the flash frequency 100 cps (Fig 2)

In one case (Figs 7 and 8) the response pattern was alternating at the frequencies between 40 cps ($\tau = 25$ msec) and 67 cps ($\tau = 15$ msec) At these frequencies the response to every second flash was found to be lower than the other responses A similar observation has been made by Best & Bohnen (1957) For higher frequencies up to 100 cps the stimulus and the response periodicity were identical in this case (Fig 8)

Three of the test subjects had an ERG periodicity of 50 cps to a flash frequency of 100 cps (Figs 5 and 6) indicating an electroretinographic response only to every second flash The curves are highly regular and this periodicity is evident in the whole stationary phase of the flicker ERG The curves are similar to but not identical with those evoked by flicker of half this frequency 50 cps as the amplitudes are slightly lower

The most direct explanation of the phenomenon seems to be that in flicker stimulation the response evoked in a retinal element fascilitates response in

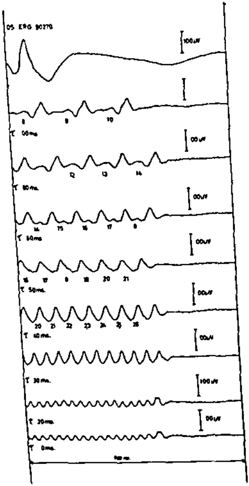


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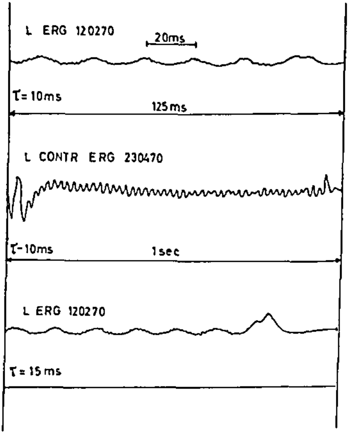


Fig 6
50 cps response pattern at a flicker frequency of 100 cps (τ = 10 msec)

any special response The amplitudes and the appearance of the waves following the last flash are similar to these parameters of the waves following the other flashes in the stationary phase of the ERG

As the frequency is further increased the amplitude of the last positive wave maintains its size while the foregoing waves gradually decrease with increasing frequencies Thereby the last positive wave stands out as an off response evoked by the termination of the flicker train as such (Figs 2 and 4) This effect is increasingly impressive with increasing flicker frequencies The phenomenon is also fully present at the highest flicker frequency used 100 cps also in those cases in which this frequency yields ERG flicker fusion (Fig 2) It is assumed that a similar off response would be found at a similar abrupt termination of continuous light

From the curves and most clearly in Fig 8 it is seen that this off response is polyphasic and consists of both positive and negative waves equally spaced

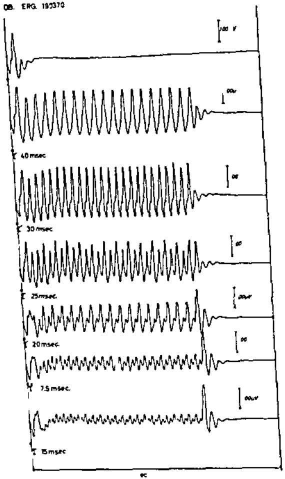


Fig 7

Alternating potentials at the flicker frequencies 40 cps (τ = 25 msec) to 67 cps (τ = 15 msec) Off response at the termination of the flicker trains at high frequencies

with a period about 30 msec The period of the off response is independent of the flicker frequency The amplitudes are rapidly decreasing and only 2–3 periods may be followed

Also the amplitudes of the waves of the off response are largely independent of the flicker frequency in spite of the fact that the average light intensity during the flicker train increases proportionally to the flicker frequency This

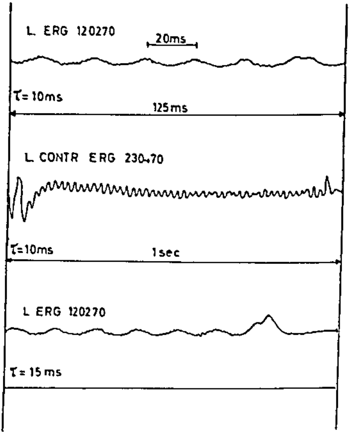


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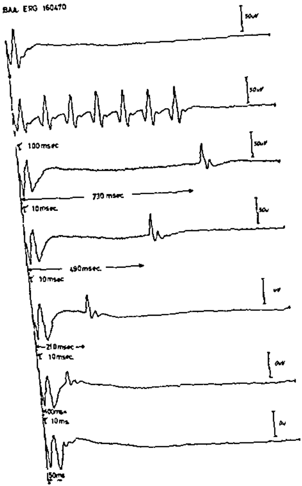


Fig 9
The off response at the termination of flicker trains of different durations

curve corresponding to the first flash *missing* that is one period after the last flash An influence on the retinal response caused by the termination of the flicker train of course cannot appear in the ERG before this point of the curve

In the series of curves recorded by gradual increase of the flicker frequency there is obviously a gradual transition from the b wave evoked by the last

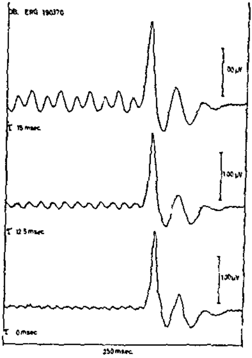


Fig 8

Off response evoked by the termination of high frequent flicker trains Alternating potentials at the flash frequency 67 cps (τ = 15 msec)

is to be expected under the assumption that the off response is determined by the intensity of the last flash and not by the average light intensity during the flicker train

The off response is only slightly influenced by shortening of the flash train when this lasts more than 2–300 msec (Figs 9 and 10) In trains shorter than that the off response is superimposed upon the initial response and seems to be reduced in size As the flicker train is further shortened there is a gradual transition from the flicker evoked ERG to the single flash ERG The trains off response is gradually changed to become similar to the waves observed in many cases at or immediately after the negative deflection following the b wave (Figs 9 and 10) Then it may be presumed that these waves may represent an off response evoked by the single flash

When dealing with the off response evoked by the termination of the flicker train as such it should be noted that this should not be related to the moment of termination of the last flash Immediately after the last flash comes only the same response pattern as after the foregoing flashes up to the point of the

flash in low frequent flicker to the off response at the termination of the flash train in higher frequencies This off response stands out not by the last wave being increased but by the foregoing waves being reduced As has been described these waves are reduced partly by the phase shift and algebraic summation of individual flash responses However the amplitude of the b wave evoked by the last flash is obviously not reduced by the superimposition of a following a wave On this background it seems reasonable to consider the off response at the termination of the train as being built up partly by a b wave evoked by the last flash

This point of view may be carried further As the off response is evident also in cases of ERG flicker fusion at a frequency of 100 cps we expect it to be identical with the off response evoked by the termination of continuous light Then by analogy also this off response may be considered as partly consisting of a b wave evoked by the ultimate part of the light near its termination At each moment during continuous light a part of the retinal elements are involved in the b wave producing process The effect is not discernible as b waves in the ERG during continuous light because of interference with consecutive potentials positive and negative produced by other retinal elements At the termination of the light the last b waves which are not interfering with later negative potentials stand out as part of the electroretinographic off response

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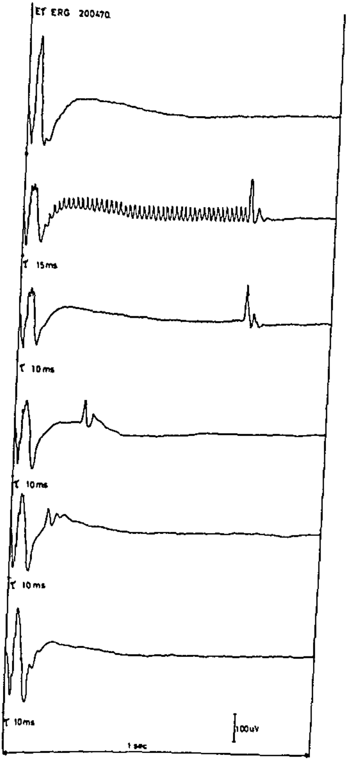


Fig 10
The off response at the termination of flicker trains of different durations

A large number of enzymes are involved in glycolysis and oxidative energy metabolism There is evidence that inhibition of aconitase activity in the citric acid cycle causes accumulation of citrate (Randle et al 1968) There is evidence also that the citrate concentration may influence the activity of the enzyme phosphofructokinase which regulates the formation of pyruvate from gluco e (Atkinson et al 1968) Furthermore it has been shown that addition of one component of this complicated equilibrium may cause the concentrations of the resulting substances in the equilibrium system to increase (Randle et al 1968) Consequently changes in enzyme activities or substrate concentrations some where in the equilibrium may be reflected in e g the pyruvate and citrate concentrations

The investigations of Gronvall (1937) indicate that pathologic changes (glau coma malignant tumours) in the eye may be accompanied by increased citrate concentration of the aqueous humour in comparison with the citrate concen tration in senile cataract In relation to cataract development changes in enzyme activities in both the Embden Meyerhof pathway and the citric acid cycle have been demonstrated (Hockwin & Berghoff 1966 Friedburg 1968) Cole (1965) showed that the energy requiring Na^{+} transport across the non pigmented epithelium of the ciliary body in pigs increased in the presence of citrate isocitrate and succinate It is therefore possible that degenerative changes in the anterior section of the eye may be reflected in the pyruvate and citrate concentrations of the aqueous humour

All the tissues with which the aqueous humour is in contact have been shown to contain enzymes necessary for glycolysis and the citric acid cycle

The present paper reports the results of determinations of the citrate and pyruvate concentrations in bovine aqueous humour and of corresponding plasma citrate concentrations

Material and Methods

The material comprises 39 cattle ranging in age from 1 to 10 years The aqueous humour was obtained by puncturing the chamber just inside the limbus corneae with a sterile subcutaneous needle immediately after the animal had been killed between 1 30 and 2 o clock p m 1–1½ ml of aqueous humour were aspirated per puncture Whether the right or the left anterior chamber was punctured depended on which side of the head was uppermost The blood samples consisted of mixed arteriovenous blood from the internal carotid and the jugular vein in the neck collected immediately after the chamber puncture All the animals appeared to have been healthy

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CITRATE AND PYRUVATE CONCENTRATIONS IN BOVINE AQUEOUS HUMOUR

BY

A BRUUN LAURSEN

The results are reported of enzymatic colorimetric determinations of citrate concentrations in aqueous humour and plasma and of pyruvate concentrations in aqueous humour from cattle aged from 1 to 10 years
The mean citrate concentration in aqueous humour samples from 32 animals was 86 5 ± 16 3 μmol/l (mean value ± standard deviation)
In plasma samples from 27 animals the mean citrate concentration was 110 3 ± 47 2 μmol/l
In aqueous humour samples from 24 of the 32 cattles the mean pyruvate concentration was 172 6 ± 35 6 μmol/l
Regression analysis revealed a relationship between age and the citrate concentrations in aqueous humour ($p < 0\ 001$) and between age and the pyruvate concentrations in aqueous humour ($0\ 05 > p > 0\ 02$) the citrate concentrations rising and the pyruvate concentrations falling with increasing age No relationship was demonstrated between the plasma citrate concentrations and age ($0\ 50 > p > 0\ 40$)

Key words aqueous humour – citrate – pyruvate – cattle (bos taurus)

Citrate and pyruvate are important intermediates in energy metabolism Both metabolites occupy key positions pyruvate being situated in the Embden Meyerhof pathway and citrate in the Krebs citric acid cycle In glycolysis pyruvate is converted into lactate In addition pyruvate may be oxidized via the citric acid cycle

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Table I

Citrate and pyruvate concentrations in bovine aqueous humour after standing at 4°C for 24 hours The samples were heated to opalescence immediately after the chamber punctures The concentrations are given in μ mol/l

Trial	1	2	3	4
Pyruvate conc	162	176	156	188
Pyruvate conc after 24 hrs	99	74	108	128
Difference in conc after 24 hrs	− 63	−102	− 48	− 60
Citrate conc	116	101	113	87
Citrate conc after 24 hrs	121	104	101	94
Difference in conc after 24 hrs	+ 5	+ 3	− 12	+ 7

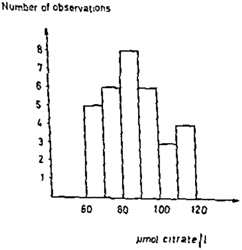


Fig 2

Distribution of the citrate concentrations in aqueous humour from 32 cattle between the ages of 1 and 10 years

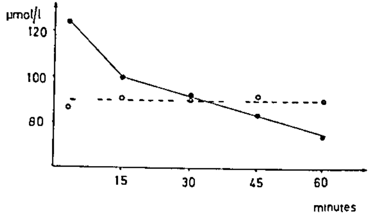


Fig 1
Citrate and pyruvate concentrations in untreated aqueous humour at room temperature The individual determinations were made on samples taken from a common pool
●——● pyruvate ○----○ citrate

The analytic method employed for both citrate and pyruvate determinations is a modification of Moellering & Gruber's (1966) enzymatic colorimetric method described by Bruun Laursen & Harbo Kristensen It was necessary to heat the aqueous humour to the degree of mild opalescence immediately after the withdrawal to prevent a decrease in the pyruvate concentration which would cease after addition of lactate dehydrogenase

Fig 1 shows curves plotted for the citrate and pyruvate concentrations in a non heated aqueous humour pool during one hour at room temperature While the citrate concentration remained unchanged the pyruvate concentration fell to 60 4 % of the starting value in the course of one hour

Four heated aqueous humour samples were followed with a view to extinc tion values for 30 minutes before the proper concentration determination was begun by addition of lactate dehydrogenase The extinctions were constant in all cases In the remaining 28 samples two or three readings within five mi nutes prior to addition of enzyme likewise displayed unchanged extinction values on samples which had been heated

Table I shows the alterations of the citrate and pyruvate concentrations after standing for 24 hours at 4°C The samples had been heated immediately after withdrawal from the animals Despite heating the pyruvate concentrations had decreased appreciably whereas the citrate concentrations remained unchanged

All determinations were duplicated

Table II

Citrate and pyruvate concentrations in bovine aqueous humour and corresponding plasma citrate concentrations arranged according to age. Concentrations are given in μ mol/l

Age of years	Citrate conc of aqueous humour	Citrate conc of plasma	Pyruvate conc of aqueous humour
1	83	101	197
	77	75	178
	69		266
2	60	94	178
	70	85	166
	72	93	
	82	138	187
	93	107	213
	60	22	234
3	74		
	84		
	64	127	169
	65		142
4	89	135	
	71	8	
	89	189	129
5	113	123	
	104	95	142
6	84	191	135
	87	92	192
	101	160	178
7	93	131	204
	94	101	130
8	96	92	
	73	44	
10	94	16	16
	96	80	105
	115	104	155
	116		162
	101	145	140
	113	123	156
	87	133	188
N	32	27	24
Mean ± SD	86.5 ± 16.3	110.3 ± 4[illegible]2	1[illegible]6 ± 3[illegible]6
Mean ± SEM	86.5 ± 2.9	110.3 ± 9.1	17[illegible]6 ± 7.5

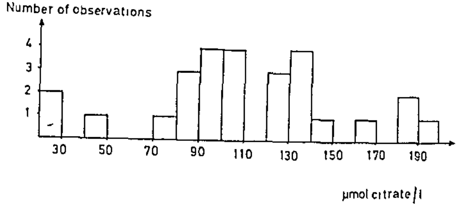


Fig 3

Distribution of the citrate concentrations in plasma from 27 cattle between the ages of 1 and 10 years

Results

The results have been set out in Table II

The distributions of the concentrations in aqueous humour and plasma are seen in Figs 2 3 and 4 The citrate concentrations in aqueous humour samples from all 32 animals averaged 86 5 ± 16 3 μ mol/l The citrate concentrations in 27 plasma samples averaged 110 3 ± 47 2 μ mol/l

Regression analysis revealed a statistically significant correlation between

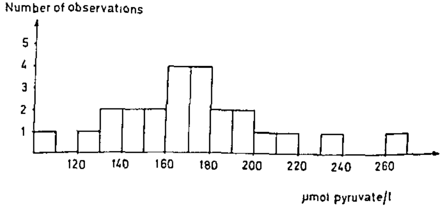


Fig 4

Distribution of the pyruvate concentrations in aqueous humour from 24 cattle between the ages of 1 and 10 years

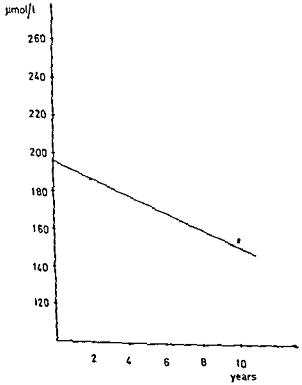


Fig. 6

Relation between the pyruvate concentrations in aqueous humour and age in 24 cattle between the ages of 1 and 10 years

$y = -4.39\,x + 196.40 \quad r = -0.4370 \quad 0.0 > p > 0.02$

The citrate concentrations found in aqueous humour from cattle between the ages of 1 and 10 years are thus in close agreement with Gronvall's results with indigotrisulphonate as indicator in aqueous humour from cattle aged from 3 to 10 years

No constant relationship seemed to exist between the individual citrate concentrations in plasma and aqueous humour (Table II) The total mean values in plasma (110.3 ± 4.9 µ mol/l) and in aqueous humour (86.5 ± 16.3 µ mol/l) suggest a higher concentration in plasma than in aqueous humour However the variances of the stated two groups differ significantly Direct statistical comparison is therefore impossible Great variations are seen in plasma both above and below the level in aqueous humour

Gronvall likewise found appreciable differences in plasma citrate concentrations within a given animal species even after ultrafiltration

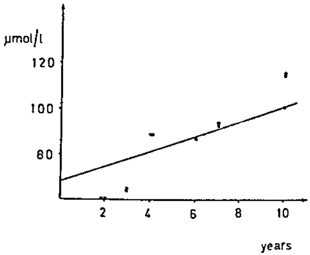


Fig 5

Relation between the citrate concentrations in aqueous humour and age in 32 cattle between the ages of 1 and 10 years $y = 3.46x + 68.46$ $r = 0.6874$ $p < 0.001$

the citrate concentrations in the aqueous humour and age ($r = 0.6874$ $p < 0.001$) the concentration rising with increasing age (Fig 5) No similar significant correlation was noticed between age and the plasma citrate concentrations ($r = 0.1387$ $0.50 > p > 0.40$)

In aqueous humour from 24 cattle the mean pyruvate concentration was 172.6 ± 35.6 µ mol/l

Regression analysis revealed a relationship between age and the pyruvate concentrations in aqueous humour the concentrations decreasing with increasing age ($r = -0.4320$ $0.05 > p > 0.02$) (Fig 6)

Discussion

Gronvall (1937) using Thunberg s technique with indigotrisulphonate as indicator found in aqueous humour of cattle ranging in age from 3 to 10 years (11 animals) a mean citrate concentration of 16.74 ± 0.47 µg/ml (87.18 ± 2.45 µ mol/l) Using methylene blue as indicator Gronvall in a series of 19 cattle between the ages of 2 months and 15 years found a mean citrate concentration in aqueous humour of 24.94 ± 0.51 µg/ml (129.8 ± 2.65 µ mol/l) In newborn calves (1–3 days old) somewhat higher values were found 19.83 ± 0.64 µg/ml of aqueous humour (10 animals) using indigotrisulphonate as indicator and 27.09 ± 0.68 µg/ml (10 animals) using methylene blue as indicator Gronvall s figures indicate mean value ± standard error while the figures in the present material indicate mean value ± standard deviation

Reim & Turss (1968) showed the decrease in the pyruvate concentration of untreated bovine aqueous humour to be accompanied by a corresponding rise of the lactate concentration

The mean pyruvate concentration found in this material of bovine aqueous humour is of the same order as that published by Reim & Turss (1968) After immediate enzyme inactivation by perchloric acid they found a pyruvate con centration of 205 0±10 8 μmol/l (mean±SD) in bovine aqueous humour

We cannot pronounce with certainty on the significance of the alterations of the citrate and pyruvate concentrations with increasing age They may be a consequence of a change of the metabolic pattern in the anterior eye section including the lens

Pohjola (1966) noticed a decreasing glucose concentration in human aqueous humour with increasing age This likewise argues in favour of an alteration in the anterior eye section with increasing age

Sippel (1965) pronounced as his opinion that with increasing age the carbo hydrate metabolism of the lens changes from anaerobic towards aerobic meta bolism with greater participation of the citric acid cycle

Stewart & Papaconstantinou (1966) demonstrated an increase of the LDH_1 fraction (lactate dehydrogenase isoenzyme 1) in bovine lens epithelium upon ageing They considered that this favoured the oxidation of pyruvate via the Krebs citric acid cycle rather than glycolysis

The apparent decreased pyruvate concentration and increased citrate con centration in bovine aqueous humour with increasing age is possibly explain able on this basis If so the citric acid cycle must increasingly draw on the pyruvate pool with increasing age while glycolysis simultaneously declines A steady state should then be attained at a higher level for citrate and at a lower level for pyruvate

Mandel & Zimmer (1952) demonstrated higher citrate and pyruvate concen trations in calf lenses than in lenses from adult cattle Murata & Hockwin (1969) also found higher citrate concentrations in calf lenses than in lenses from adult cattle Mendel & Zimmer s observations indicate that the decrease in the pyru vate content of the bovine aqueous humour upon ageing may be associated with changes in the metabolism of the lens Changes in cellular permeability only would not explain the differing changes of the citrate and pyruvate con centrations in the aqueous humour with increasing age

Acknowledgments

This study was aided by a grant from Cykelhandler P Th Rasmussen og hu stru Alma Rasmussens Mindelegat The author wishes to thank Dr K J Gra

In the present material the citrate concentrations in aqueous humour were seen to increase significantly with age whereas in plasma they did not

Using indigotrisulphonate as indicator Gronvall found the serum citrate concentrations in 11 cattle between the ages of 3 and 10 years to average 33 15 ± 1 10 μg/ml (172 7 ± 5 7 μmol/l) and in 10 calves (1–3 days old) it averaged 40 32 ± 2 58 μg/ml

Grönvall also noticed extensive similarity of the citrate concentrations in ultrafiltered serum and aqueous humour from different animals (horse pig sheep rabbit and guinea pig) He believed this to be attributable to linkage of part of the serum citrate to protein because he found much lower citrate values in ultrafiltered serum than in corresponding non ultrafiltered serum There is however no reason to suppose (nor did Gronvall) that the sensitive regulation mechanism concerning citrate concentration in aqueous humour suggested by him depends on an equalisation of concentrations by simple diffusion between aqueous humour and ultrafiltered plasma The fact that in the present material some plasma citrate concentrations were equal to or lower than *the corresponding citrate concentrations in aqueous humour argues* against this hypothesis

Though the blood samples used consisted of arterial and venous blood in different proportions and Lenner (1934) found about 16 % less citrate in venous than in arterial blood from the human uterus the variations in the plasma citrate concentrations found in the present material seem to be too great to be attributable to differences in the proportion of venous and arterial blood in the samples Haemolysis or erythrocyte content in the plasma may be responsible for the greater variations though this is not likely The fact that the animals were not fasting may account for part of the variation

Incidentally the pyruvate concentrations in aqueous humour were characterized also by a very considerable standard deviation This may be due to glycolysis to some extent as well as to variation with age Therefore the pyruvate concentrations found in this material are doubtless minimum values A moderate decrease in concentration occurs during the short interval before heating and after heating of the aqueous humour a slow decrease of the pyruvate concentration takes place apparently of the *order of 2–4 μmol/l* per hour (Table I) The determinations in the present study were all made within 3–3½ hours of killing The decrease in pyruvate concentration due to glycolysis must accordingly be limited

Differences of breed which cannot be avoided in slaughterhouse material may account for part of the variations of the concentrations though Gronvall (1937) found very small differences between the citrate concentrations of the aqueous and serum of cattle of very different breeds

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A CASE OF OPTIC DISC ANGIOMA
With a fluorescein angiography

BY

K LANDBO

A case of optic disc angioma in one eye of a middle aged woman is reported. The angioma did not show any sign of progression and there were no neurological symptoms. A fluorescein angiography was carried out showing that the angioma was filled simultaneously with the retinal arteries. It is believable that not all optic disc angiomas should be named von Hippel tumors.

Key words angioma – optic disc – Von Hippel – fluorescein *angiography*

Angiomas of the optic disc are not frequently reported. Darr et al. (1966) who reported the only bilateral case of juxtapapillary retinal hemangiomas found 14 recorded unilateral cases. Six more cases have been reported by Cibis (1965), Laufique et al. (1966), Litricin (1967), Manshot (1968) and Thomas et al. (1970).

In his Tumors of the Eye Reese (1963) emphasizes that von Hippel's disease may manifest itself as an angioma of the disc instead of the retina although this is not generally appreciated. In the cases reported by Carr & Stallard (1933), Cross (1943), Souders (1949), Wallner & Moorman (1955), Manschot (1968) and Thomas et al. (1970) there were no neurological symptoms and also in the present case the angioma was an isolated finding.

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vesen for allowing this work to be performed at the Department of Clinical Chemistry, Centralsygehuset Esbjerg

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A CASE OF OPTIC DISC ANGIOMA

With a fluorescein angiography

BY

K LANDBO

A case of optic d sc angioma in one eye of a middle aged woman is reported The angioma di l not show any sign of progression and there were no neurological symptoms A fluorescein angiography was carried out showing that the an ioma was filled simultaneously with the retinal arteries It is believable that not all optic disc angiomas should be named von Hippel turr ors

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Fig 1
Color photography of the right eye fundus
The angioma is situated at the disc margin at the 1 o clock position

In the following report a fluoresceinographic study has been carried out in the attempt to show whether the angioma was fed by the retinal or the ciliary vessels

Case Report

The patient was a 46 year old woman who had been admitted to the Department of Neurology because of hemicrania

There was no family history of neurological diseases The patient had since the age of 14 years complained of a left sided headache which used to arrive with intervals of weeks or months and lasted about twenty four hours For the last two years the headache had been present two or three times weekly In relation to the attacks of hemicrania the visual acuity of both eyes was lessened but always cleared up when the headache disappeared The patient also complained of pains located in the muscles of the neck and shoulders and occasionally in the lower back

Neurological examination of the patient was normal

Plain X ray of the skull was normal

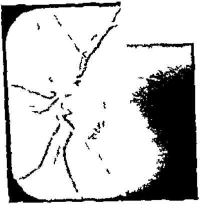
Left carotid and vertebral angiography did not reveal any abnormalities

Ophthalmological findings

Visual acuity of both eyes 1 0 emmetropia

Slit lamp examination and perimetry (2000 white of both eyes were normal

Ophthalmoscopy of both eyes The optic discs were of normal size shape and color The macular areas were normal and so were the arteries and veins There were no exudates or hemorrhages At the margin of the right disc at the 1 o clock position was



Fig

Color fluorescein angiography of the right eye fundus *Early arterial phase*
The angioma is situated at the disc margin at the 1 o clock position.

een an angioma (Fig 1) which was obviously sitting upon a short stalk The color was pink The surface was glistening and woolly with many small vessels visible It was not possible to see the vessels feeding the angioma The retinal vessels were passing beneath the angioma without changing calibre or direction The same findings ere obtained by means of the Hruby lens There were no opacities in the vitreous
A fluorescein angiography of the ri ht eye fundus (Fig 2) showed that the angioma as filled simultaneously with the retinal vessels In the later phases some leakage fr m the angi ma occurred
The angioma was observed by an ophthalmologist 1 -1 years ago It was controlled by him for several years nd did n t change Recently the s me ophthalmologist exam ned the pat ent aga n nd he still fo nd the angioma unchanged

Comments

It is shown elsewhere in fluoresceinographic studies that the angiomas in von Hippel s disease when situated in the periphery and with big afferent and efferent vessels visible are filled from the retinal arteries In the cases of angiomas located on the optic disc or at the margin of the optic disc it is not possible to see the feeding vessels and so far no attempt has been made to show whether the optic disc angiomas are fed from sources other than the central retinal artery which might allow us to make a distinction between these angiomas and von Hippel s angiomatosis
In the report of Manschot (1968) the histologic examination of the angioma

at the disc showed that the "nearest retinal artery had no relation to the tumor

The fluorescein angiography in the present case did not allow us to make any conclusion whether the angioma was fed by the retinal or the ciliary vessels Using a camera with time intervals shorter than 1 second between the pictures which was the adjustment of our camera the result might be different

The angiomas in von Hippel s disease usually show progression with exudation resulting in decreased visual acuity Among the 20 cases of angiomas on the optic disc or at the margin of the optic disc reported since 1933 only one case Wallner & Moorman (1955) did not show progression nor in the present case has there been any sign of progression It is believable that some differences concerning pathogenesis pathology and prognosis may exist between those disc angiomas which show progression and those which do not The latter ones including the angioma in the present case should not be named von Hippel tumours without some hesitation

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confirmed that they predispose to cataract development In 1948 Dunnington warned against the filtering operations on these grounds At the ophthalmology congress in 1954 Sourdille stated in his introductory address on operative glaucoma therapy that opacities in the lens are especially frequent in glaucoma and the acceleration of cataract development after filtering operations is indisputable

There have been different opinions about the treatment of glaucoma eyes with cataract A common method has been to operate the glaucoma first and later the cataract a combined operation has also had its adherents In more recent times some surgeons have held that the cataract operation in itself gives adequate pressure reduction in many simple glaucoma eyes

In the majority of cases however the glaucoma operation must be performed at a time when a cataract operation cannot yet be considered If cataract operation later becomes necessary it must be performed on an eye with a filtration bleb In this situation some surgeons choose to make the incision at the (o clock position others inferotemporal but the majority make a superior corneal incision at 12 o clock in order to save the filtration bleb

Experience of the effects of these cataract operations on the subsequent pressure in the eye has been quite varied

Dyson (1968) found some worsening of the pressure conditions with inferotemporal incisions Medication became necessary in 2 of 9 eyes preoperatively pressure regulated without treatment and 1 of 6 eyes previously pressure controlled by medication required repeated operation

Callahan (1957) has also had unsatisfactory experiences after operation with infero lateral incision 9 of 14 eyes required medication or operative treatment while before the operation 5 of 15 had used medication

Randolph Maumenee & Iliff (1971) sum up their experience with 46 eyes thus Cataract extraction after a filtering procedure has little if any influence on the course of glaucoma the encouragingly low or normal pressure shortly after the operation rising in the course of 6–8 months to 30 mm or more The operational method is not described

Boyd (1969) finds that irrespective of where the incision was located 50% of the eyes which preoperatively needed no treatment after operation required it and the eyes which had required medication preoperatively needed stronger medication after operation

Yasuna (1964) reports experiences with 26 eyes first operated with iridencleisis and later operated for cataract with superior incision without regard to the filtering bleb Eighteen eyes had a somewhat lower pressure than before the cataract operation 3 a somewhat higher pressure and all could be held by medication at 4 mmHg or below but ? had periods with rising pressure

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INFLUENCE OF CATARACT OPERATION ON THE PRESSURE IN GLAUCOMA EYES OPERATED WITH IRIDENCLEISIS

BY

PER RIISE

Eighty nine glaucomatous eyes which had been operated with Holth s iridencleisis later underwent cataract extraction performed by the superior route to retain the filtering area Of these eyes 62 were prior to the cataract extraction normo or hypotensive without medication and none of these eyes became hypertensive postoperatively nor was antiglaucomatous treatment needed

The remaining 27 eyes were receiving antiglaucomatous medication prior to the cataract extraction After the cataract extraction ocular tension increased by more than 5 mmHg in 2 eyes remained at approximately the same level in 4 eyes and decreased to normal values without medication in 21 eyes

In the whole material only 6 eyes needed antiglaucomatous medication after cataract extraction Cataract operation in glaucomatous eyes previously operated by Holth s iridencleisis had a tendency to normalize the ocular tension in both hypertensive and hypotensive eyes

Key words surgery – iridencleisis – cataract extraction – glaucoma – intraocular tension

Filtering operations for simple glaucoma are usually performed on an age group with a high cataract incidence which may explain why these operations were carried out for several decades without provoking the suspicion later

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Results

Group 1

Eyes which were pressure regulated before the cataract operation without medication — 62 eyes

(A) The pressure increased more than 5 mm after the cataract operation — 10 eyes

The pressure here was on average 9 mm pre operative and 16 4 mm post operative All these eyes were post operatively pressure regulated without medication

(B) The pressure varied less than 5 mm pre and post operative — 41 eyes

The pressure here was on average 12 9 mm pre operative and 12 6 mm post operative All these eyes were pressure regulated without medication

(C) The pressure was reduced by more than 5 mm after the cataract operation — 11 eyes

The pressure here was on average 19 6 mm pre operative and 10 7 post operative All these eyes were pressure regulated without medication

Group 2

Eyes which were treated with medication before the cataract operation — 27 eyes

(A) The pressure increased by more than 5 mm after the cataract operation — 2 eyes

The pressure before the operation with treatment averaged 15 mm and after the operation 23 mm one eye with and one eye without treatment

(B) The pressure with treatment before and after the operation varied less than 5 mm

The pressure with treatment before and after the operation averaged 18 3 mm and 18.5 mm respectively all eyes being pressure regulated by treatment

(C) Treatment which had been necessary before the cataract operation could be suspended after the operation — 21 eyes

The pressure prior to the cataract operation was with treatment an average of 19.3 mm and subsequent to the operation without treatment an average of 12 8 mm All these eyes were subsequently pressure regulated without treatment

Vorosmarthy & Ballschuh (1968) find on the basis of 37 eyes operated by superior corneal incision that cataract operation in most cases has the effect of reducing the pressure Their groups with respectively the highest and the lowest pressures preoperatively were both smaller after the operation

Scheie (1956) describes his modification of cataract operation with superior corneal incision and sums up his experience with 22 eyes previously operated by iridencleisis or corneoscleral trephining thus No eye developed a subsequent rise in ocular tension or needed miotics

Regan & Day (1971) operated without regard to the filtering bleb 70 eyes previously subjected to filtering procedures After the operation 53 eyes had pressures under 20 mmHg 13 had between 20 and 30 mmHg and 4 had over 30 mmHg

Laatikainen (1971) found in 32 cases with previous antiglaucomatous surgery no distinct effect of lens extraction on the intraocular pressure

A clarification of this question will provide more reliable indications in the therapy of glaucoma I have therefore examined the material I have on eyes first operated with iridencleisis and later for cataract

Material

My material is glaucoma eyes previously operated with iridencleisis and later for cataract in St Torfinn s Eye Clinic Hamar Norway in the years 1954–68 a total of 112 eyes In 28 cases there is no record of the pressure more than 3 months after the operation for cataract so only the remaining 89 eyes will be considered

Methods

Operational methods were the following incision with Graefe knife puncture and counter puncture with small limbus based conjunctival flap as in un complicated senile cataract cases but the incision was completed in free cornea at 12 o clock without a conjunctival flap The lens was removed in the earlier years by capsule forceps later by erisophake intracapsular in 84 cases and involuntarily extracapsular in 5 cases No iridectomy

The pressure is measured with Schiotz s original tonometer and converted to mmHg followings Friedenwalds 1955 curve where scale unit 4 with weight 5.5 is taken as 24.4 mm and this is set as the upper limit for normal pressure The margin for noting similar or varying pressures is set at 5 mmHg

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Alterations in the pressure in the years immediately after cataract operation on eyes previously operated by iridencleisis

Iliff, Maumenee & Randolph (1971) find that the encouragingly low or normal tension initially found after a cataract extraction rises in 6 or 8 months to a level of 30 mmHg or more

My *material shows no such tendency from the first pressure measurement* after 3 months till the first measurement after 3 years following the cataract operation Such information is available in respect of 46 eyes of which 4 showed *significant* pressure increase 10 had a significant reduction and 32 *showed no significant alteration (Margin for significant pressure alteration* was set at 5 mmHg)

Conclusion

An unfavourable pressure increase after cataract operation on eyes previously operated by iridencleisis was demonstrated in 2 of 89 eyes a desirable decrease in 21 eyes

The figures shown in the tabled results indicate that cataract operations in eyes previously subjected to filtering operations have a tendency to increase the pressure in eyes which previous to the operation had the lowest pressure and to lower the pressure in eyes which preoperatively *had the highest pressure* The statistics of Vorosmarthys & Ballschuh (1968) show the same tendency

My impression (as yet unsupported statistically) is that the filtration blebs generally have the same appearance before and after the cataract operation

I feel that the cause of the changes of pressure is not to be found *in changes* in the filtration bleb

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fying and recording apparatus generally differs from one investigator to another Usually an EEG recorder – modified more or less – is used giving an often unreliable AC registration of a potential which essentially is a DC voltage

Dr Gliem's monograph subtitled Ein Erfahrungsbericht is a most comprehensive study in clinical EOG beginning with some methodological investigations Among the notable findings in this section is that the so called dark trough will appear after a rather constant interval of time independent of any change in light intensity

Thereafter a normal material is presented in which the EOG and ERG parameters are thoroughly analyzed statistically

Lastly various pathological conditions in the retina are examined with EOG and ERG Enumeration would be confusing but the value of using both techniques must be emphasized

This book fulfils a purpose both as an introduction to the topic and as a manual with an extensive bibliography It can be recommended as absolutely necessary for anyone interested in the electrophysiology of the eye

Erik Krogh

Havener William H Synopsis of Ophthalmology 3rd edition C. V Mosby St Louis 1971 553 pages 35 illustrations Price $ 19 75

This extremely useful book is written for the practicing physician and clearly demonstrates the author's knowledge of and talent for teaching explanation and planning The book is arranged in terms of functional categories rather than the usually preferred anatomical classification

As fundus inspection is the most valuable contribution ophthalmology can offer colleagues an impressive part of the book concerns itself with *instruction and interpretation* of ophthalmoscopy and should appeal to the irresistible urge to gain skill in fundus inspection In 91 chapters the function of the whole *ocular* system and its disorders and diseases are presented properly and wisely Special chapters deal with ocular therapy *value of consultation* and referral and prevention of blindness Of the many available books with the same aim Havener's Synopsis should certainly be preferred by many

P Brændstrup

Casey T A Corneal Grafting Butterworth London 1972 340 pages Price £ 10 00

This is an easily read book covering various topics of corneal grafting and comprises the most refined techniques of prosthokeratoplasty with bolt and nut (described by Cardona Castroviejo and de Voe) and a new modification of osteo dendro kerato prothesis (Strampelli and Marchi)

The book deals also with many details concerning the common graft technique (preplaced overlay sutures air only temporary in the anterior chamber in perforatin keratoplasty and details of lamellar grafts (Paufique) A special chapter concerns combined cataract extraction and corneal graft (Casey)

Valuable chapters deal with wound healing (Anseth) immunological aspects (French) and measuring of endothelial viability both microscopically and by vital staining with critical remarks on dye exclusion tests and enzymatic dye tests (O Neill)

Refractive keratoplasty (keratomileusis and keratophakia) also has a chapter for itself

Ruben contributes a valuable discussion of contact lenses after grafting (corneal and scleral moulded lens splint soft lens) and interesting remarks on astigmatism after grafting

There are many illustrations of high quality also in colour and the text is well written and well selected

The book is recommended *M S Norn*

Christman Ernest H A Primer on Refraction Charles C Thomas Springfield Illinois 1972 120 pages 71 figures Price $ 4 50

This little pocket sized book is designed primarily for the resident in ophthalmology It deals with subjective refraction cross cylinder the sun duochrome test lensometer streak retinoscopy muscle balance prisms etc

Keratometry and senile inverse astigmatism are not mentioned

The representation is good with many instructive sketches and the explanation of retinoscopy is simple and excellent

The book is recommended *M S Norn*

Gliem Hans Das Elektrookulogram Ein Erfahrungsbereicht VEB Georg Thieme Leipzig 1971 106 pages Price DM 35

Clinical electrooculography (EOG) can be defined as an indirect measurement of the standing corneo retinal potential and its slow variation with changes in light intensity

Although in some cases *EOG is definitely more sensitive than ERG* in disclosing retinal pathology it has as yet to be accepted as a relatively reliable clinical test This is due primarily to the appreciable intra and interindividual variation of the recorded potentials Various arithmetical tricks e g elimination of the absolute values by percentage statements – will yield only an apparent enhancement of numerical significance

Another factor which makes evaluation and comparison difficult is that the ampli

From the Dalby Health Service Research Center
(Head Åke Nordén Prof M D) Hälsovårdscentralen Dalby and
The Department of Experimental Ophthalmology
(Head C E T Krakau Prof M D) Universitetet Lund Sweden

COMPARISON OF SCHIÖTZ AND GOLDMANN TONOMETRY IN A POPULATION

BY

BO BENGTSSON

Schiotz tonometers are still used widely for routine tonometry and glau coma screening Appreciation of the inaccuracy of impression tonometry has led to a general agreement that Schiotz tonometry should be supple mented by applanation tonometry In a material of paired Schiotz and Goldmann measurements we found that about every fifth individual with an applanation pressure of over 20 5 mmHg would have been missed even if all persons with Schiotz readings lower than 7 0/7.5 were applanated Further extension of Goldmann tonometry to pat ents with still higher Schiotz readings was found to be unwarranted We concluded that the usefulness of Schiotz tonometry for glaucoma screening should be doubted

Key words population study – Schiotz tonometry – Goldmann tonometry glaucoma screening

Theoretical considerations experimental findings and practical experience unanimously indicate a high degree of precision and accuracy in the clinical use of the Goldmann tonometer (Goldmann & Schmidt 1957b Gloster 1965) Ad mittedly applanation readings are not perfectly repeatable but they have been accepted as the best means of estimating intraocular pressure in practice

Impression tonometry is generally considered to be less reliable The charac teristics of impression tonometers certified by the manufacturers vary widely (Armaly 1960) Even skilled observers make considerable errors in application

Rece ed March 19

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Reliable paired readings were obtained in 1561 cases (3106 eyes) Their age and sex distribution are given in Table I The whole material was used as an introductory part of the investigation intended to describe some pertinent aspects of the relationship between Schiotz and Goldmann tonometry Persons less than 40 years old or already subject to antiglaucomatous treatment (eight cases) were excluded from the second part which concerned the possible con sequences of certain modifications in the present practice of tonometry A total of 689 cases remained

Methods

Visual acuity ophthalmometry slit lamp examination Goldmann tonometry Schiotz tonometry sphygmomanometric measurements of the systemic blood pressure ophthalmoscopy in mydriasis subjective refraction in cycloplegia and fundus photography were all attempted in every case *Conventional equipment* was used according to a fixed *program*

The *applanation tonometry* was performed by one ophthalmologist using a Goldmann tonometer mounted on a Haag Streit 900 slit lamp The tonometer was tested at PTB in Berlin and found to be completely devoid of demonstrable

Table I
Number of men and women examined in different age groups

Age (years)	Men	Women
5–9	5	26
10–19	1[illegible]	115
20–29	12	141
30–39	153	155
40–49	115	110
50–59	93	91
60–69	84	81
70–79	59	58
80–	11	15
Total (> 40)	7 1 (347)	90 (355)

and reading of Schiötz tonometers (Gloster 1965) Individual variations in the physical properties of the cornea in the size of the globe, in the distensibility of the corneo scleral envelope and in the cushioning effect of the uveal circulation cause serious disturbances in the relationship between Schiotz readings and ocular tension

Drawing up a special calibration scale for each individual tonometer as suggested by Armaly (1960) seems impracticable Repeated tonometry cannot readily be recommended to counteract observed errors since it causes a marked decrease in intra ocular pressure (For reference see Krakau & Wilke 1971) Highly myopic eyes and eyes that have been operated on have low ocular rigidities but in normal eyes deviations from the average are unpredictable Measurements of ocular rigidity by differential impression tonometry suffer badly from lack of precision (Goldmann & Schmidt 1957a)

Nevertheless Schiötz tonometers are still widely used for routine tonometry and glaucoma screening even if it is now generally agreed that verification of positive cases by applanation tonometry should be a prerequisite to further action The present report was initiated when the author found himself unable to get a relevant answer to the question of which cases should be considered positive To be more specific it was decided to try to determine what screening level expressed in Schiotz readings should be applied in order to assure the identification with a reasonable degree of certainty of persons with a given borderline applanation pressure using current methods of examination in an unselected population

Material

The material was derived from a general ophthalmic population survey which was carried out at the Dalby Health Center in southern Sweden from March 1969 to April 1970

Invitations with a brief questionnaire were mailed in rotation following a directory to all persons aged 8 years or more who had been resident in the village surrounding the Health Center since December 1968 Out of 1917 persons invited 1702 (88.8 per cent) took part in the study

Information about persons who failed to appear or were not examined by Goldmann tonometry has been given in an earlier report (Bengtsson 1972)

Reliable applanation readings were obtained in 1644 cases Among them Schiötz tonometry usually because of unsatisfactory cooperation was not performed in 88 cases – 58 men and 30 women (all except for one man and eleven women were younger than 40 years old)

Table II

The distribution of paired Schiotz and Goldmann readings on 3106 eyes

Goldmann readings	Schiotz tonometer readings											Total
	≤4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	≥9.5	
≥28	3	1										4
27		3										3
26	1	1		2	1	1						6
25				1								1
24		1		2		1						4
23		1		4		3	1	1				10
22		1	1	3								5
21		1		2	1	3						7
20				2	3	19		8	1	1		54
19		1		17	3	50		13		8		92
18				15	1	63	5	40	3	17	5	149
17				6	4	99	21	96	10	31	14	281
16				2	2	111	10	133	13	59	28	369
15				2		65	0	193	13	111	66	470
14				2		39	8	141	14	151	80	435
13					1	19	7	106	11	165	133	442
12						6	3	38	11	139	160	377
11						1	1	13	7	81	192	295
10								4		29	60	99
9								2		9	41	52
8										1	18	19
7											1	1
6											1	1
Total	4	10	1	60	16	450	5[illegible]	813	83	802	735	3106

errors in the pertinent pressure range (For method see Jessen 1969) The right eye was always measured first the instrument was read to the nearest millimeter and the first reliable reading was recorded

The *impression tonometry* was performed by one nurse using two Schiotz *tonometers The first tonometer (manufactured and certified by SKLAR)* was used up until November 1969 when it was replaced by a second tonometer (manufactured by Winter) which had been tested and approved by PTB in Berlin (For method see Jessen 1969) The SKLAR tonometer was later tested at the tonometer station in Uppsala and found to be fit for routine use

In order to get a continuous variable the same tonometer weight had to be used in all cases A plunger load of 7 5 g was chosen since it was expected to offer the most useful pressure range considering that only readings between 3 0 and 10 0 were to be used (Moses & Hahn 1958 Friedenwald 1954) In fact no readings smaller than 3 0 were encountered (using the 7 5 g plunger load) and for technical reasons readings larger than 9 0 were not recorded separately

The right eye was measured before the left The first successful application of the tonometer in each eye was used The nurse had been instructed to read the tonometer to the nearest half of a scale division

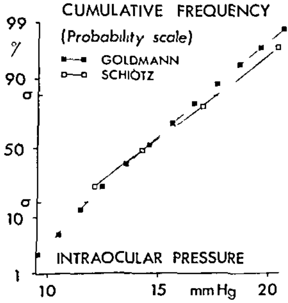


Fig 1

Cumulative frequency distribution of Schiotz and Goldmann readings in 3106 eyes Friedenwald s 1955 calibration scale was used to transform Schiotz readings into absolute terms of millimeters of mercury

Table II

The distribution of paired Schiotz and Goldmann readings on 3106 eyes

Goldmann reading	Schiotz tonometer readings											Total
	≤ 4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	≥ 9.5	
≥ 8	3	1										4
7		3										3
6	1	1		2	1	1						6
5				1								1
4		1		2		1						4
3		1		4		3	1	1				10
2		1	1	3								5
21		1		2	1	3						7
20				7	3	19		8	1	1		54
19		1		17	3	50		13		8		97
18				15	1	63	5	40	3	17	5	149
17				6	4	99	21	96	10	31	14	281
16				2	2	111	16	138	13	59	28	369
15				2		65	20	193	13	111	66	470
14				7		39	8	141	14	151	80	495
13					1	19	7	106	11	105	133	442
12						6	3	58	11	139	160	377
11						1	1	13	7	81	122	225
10								4		29	66	99
9								2		9	41	59
8										1	18	19
7											1	1
6											1	1
Total	4	10	1	50	16	450	92	813	83	502	735	3106

Results

The primary material is given in Table II

The frequency distributions of pressure readings obtained with the two types of tonometers were similar in the present population as can be seen from Fig 1 in which Friedenwald s 1955 calibration has been used to transform the Schiotz readings The median values were identical (14 3 mmHg) but the dispersion was slightly greater with the Schiötz tonometer than with the Goldmann tonometer

It is already evident from Table II that the two methods often gave quite different results in the same eye This is further illustrated in Fig 2 from which it can be seen that the distribution of applanation readings among eyes with the modal Schiötz reading 8 0/7 5 (scale reading/plunger load) was similar to that in the total material At the same time clearly increased (26 mmHg) as well as quite normal (14 mmHg) applanation values were encountered among eyes with one and the same borderline Schiötz value (6 0/7 5)

Finding an adequate description of the variations in distribution of Schiotz readings with applanation pressure presented certain difficulties A marked digit preference

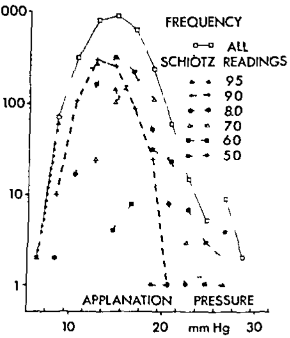


Fig 2

Frequency distribution of applanation readings in the total material and in eyes with certain Schiotz readings

favouring whole Schiotz scale divisions had to be taken into account when assigning values to the class boundaries A regression analysis with Schiotz readings as the dependent variable was rendered impossible by the existence of indeterminate Schiotz readings (≥ 9.5) in eyes with applanation pressures as high as 18 mmHg A major part of the material was brought to bear upon the essential points however by plotting su ted quantiles expressed in Schiotz readings against applanation pressure (Fig 3) – the quantile values being determined graphically from approximately linear frequency d str butions exemplified in Fig 4

Fig 3 shows that the average Schiotz pressure in eyes with high Goldmann readings was lower than predicted by the 1955 calibration scale The ranges of Schiotz readings between the 50th and 90th percentiles in eyes with identical Goldmann readings were more than one scale unit For eyes with borderline applanation pressures the distance between the 90th percentile and the 1955 calibration scale was about one and a half scale units

Fig 3 suggests that eyes with Schiotz readings as high* as 8 0/7.5 should be suspected of having increased Goldman readings Obviously the original approach to the selec tion by Schiotz tonometry of candidates for applanation had to be altered It was

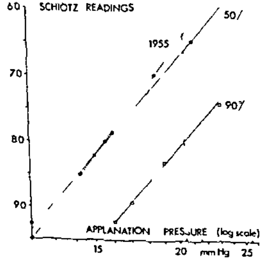


Fig 3

Pl t of ar ati ns in stated quantile values (expressed in Schiotz read ngs) with ap planat n pressure Straight lines have been fitted by hand to the points Friedenwald s 19 cal bration scale has been included for comparison.

* te that h gh Schi tz readings mean low Schiotz pres ures

replaced by an assessment of possible consequences in practice of adjustments to the screening level for Schiotz tonometry supplemented by Goldmann tonometry For this reason it was decided to use only data from persons aged 40 years or more and not treated for glaucoma or ocular hypertension The eye with the highest tension according to the method in question was chosen to represent the individual

Individuals with Goldmann readings higher than 20 5 mmHg were "concentrated" among those with Schiötz readings lower than 7 0/7 5 but diluted among those with Schiötz readings on both eyes higher than 6 5/7 5 (Table III left) Persons with 6 5/7 5 are usually considered normal since Friedenwald's 1955 calibration scale gives a corresponding intraocular pressure of 20 1 mmHg but our data indicate that they have "high" Goldmann readings often enough to support the opinion that they should be applanated in order to reduce the number of false negatives People with 7 0/7 5 on the other hand had to be considered negative since the estimated probability of finding an individual with a "high" applanation pressure was not greater among them than among people in general

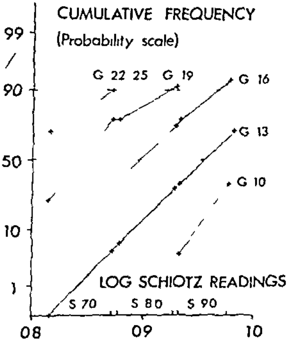


Fig 4

Cumulative frequency distribution of Schiotz readings in eyes with certain stated Goldmann readings The class widths have been modified according to the average digit preference in the total material

Table III
Efficiency of Schiotz tonometry

Goldmann tonometry (mmHg)	Schiotz tonometry (scale readings)							
	< 6 0	6 0	6 5	7 0	> 7 0	Total	≤ 6 5	≥ 7 0
> 0 5 (> 3 5) < 0 5	11 (8) 0	6 (?) ~2	9 (1) 8	4 (1) 134	1 (0) 501	24 (12) 665	19 (11) 30	5 (1) 635
Total	11	28	10	138	50?	689	49	640

The numler of persons with high applanation pressures in different groups characterized by their Schiotz readings The eye having the highest tension according to the method in question was chosen to represent the individual Only persons aged 40 years or more and not treated for glaucoma or ocular hypertension were included in this Table

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Individuals with Goldmann readings higher than 20 5 mmHg were concentrated" among those with Schiötz readings lower than 7 0/7 5 but diluted among those with Schiötz readings on both eyes higher than 6 5/7 5 (Table III left) Persons with 6 5/7 5 are usually considered normal since Friedenwald's 1955 calibration scale gives a corresponding intraocular pressure of 20 1 mmHg but our data indicate that they have "high" Goldmann readings often *enough to support the opinion that they should be applanated* in order to reduce the number of false negatives People with 7 0/7 5 on the other hand had to be considered negative since the estimated probability of finding an individual with a "high" applanation pressure was not greater among them than among people in general

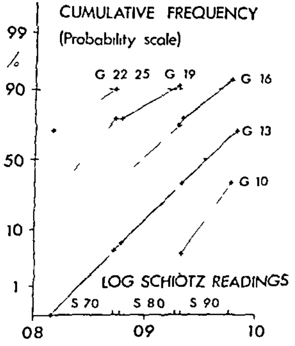


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	< 6.0	6.0	6.5	7.0	> 7.0	Total	≤ 6.5	≥ 7.0
> 20.5 (> 23.5)	11 (8)	6 (2)	(1)	4 (1)	1 (0)	24 (12)	19 (11)	5 (1)
< 20.5	0	22	8	134	501	665	30	635
Total	11	28	10	138	502	689	49	640

The number of persons with high applanation pressures in different groups characterized by their Schiotz readings. The eye having the h gh est tens n according to the method in question was chosen to represent the individual. Only persons aged 40 years or more and not treated for glaucoma or ocular hypertension were included in this Table.

The finding that persons with "high" applanation pressures were scarce among people with Schiötz readings over 6 5/7 5 did not imply that individuals with Schiötz readings over 6 5/7 5 were scarce among persons with high applanation pressures On the contrary one third of those with applanation pressures between 20 5 and 23 5 mmHg or one fifth of all those with applanation pressures over 20 5 mmHg would have been missed even if all persons with Schiötz readings lower than 7 0/7 5 had been classified as positive (Table III right) Nevertheless at the same time about 60 per cent of Schiotz positives defined in this way had normal" Goldmann readings

Discussion

The distressing fact that Schiotz and Goldmann tonometers often give quite different results in the same eye has been emphasized repeatedly (Goldmann & Schmidt 1957a Armaly 1960 Smith 1964 Anderson & Grant 1970) The Schiötz – Goldmann disparities in our material were of the same order of magnitude as those reported in earlier studies – where excessive artefacts in technique or instrumentation have been ruled out – in spite of our deliberate selection of more common methods of examination

Aiming at a calibration scale for tonographic purposes Anderson & Grant made the applanation readings with the subjects lying on their backs thus eliminating errors due to changes in posture Their ranges each including the Goldmann readings of 95 per cent of the eyes with a given Schiotz reading were however actually wider than those in our material More careful comparisons with other reports are invalidated by the unfortunate custom of describing Schiotz Goldmann disparities in an indirect way dependent on assumptions concerning the relevancy of calibration scales

A surprising feature of earlier reports has been that the standard deviation of Schiötz readings has not been markedly greater than that for the Goldmann readings (For reference and discussion see Gloster 1965) When judged from plots of the distributions on probability paper however the difference in dispersion between the two methods in our material seemed quite sufficient to support the general opinion cited in the introduction that applanation tonometry is subject to considerably less variation than impression tonometry (Fig 1)

Again more careful comparisons were invalidated – both by the possibility of small errors in the slope of the calibration scale and by the fact that intraocular pressure and ocular rigidity are not independent variables (according to unpublished data from our survey)

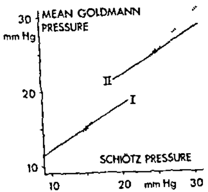


Fig 5

Schematic representation of expected variations in mean Goldmann pressure with Schiotz pressure in two hypothetical populations (I and II) with different means (15 and 9 mmHg) – supposing that the regression coefficient = $r \times \frac{\sigma \text{ appl}}{\sigma \text{ Schiotz}}$ = 0 6 in both populations

The dotted line indicates the theoretical relationship between Schiotz and Goldmann pressures

Regression curves which are often used to describe the results of past comparisons between Schiotz and Goldmann tonometry deviate greatly from the 1955 calibration scale (Armaly 1960 Anderson & Grant 1970) The position of such curves is affected by changes in the average intraocular pressure of the population examined (Fig 5) It is important to realize that such aberrations so called regression effects are an inevitable consequence of the disagreement between the two methods They provide no reason to believe that Friedenwald s calibration scale of 1955 can be substantially improved In fact the averages of all paired Schiotz and Goldmann readings in a population can confidently be expected to be more or less identical if the 1955 calibration scale is used to convert Schiotz readings into units comparable with Goldmann readings Most earlier differences in this respect can be explained by the influence of posture on the episcleral venous pressure or by the regression effect in materials selected with one of the tonometers (Levene 1971)

The values given by the conventional calibration scale are strictly speaking applicable *only* to the average Schiotz reading of the population in question The average intraocular pressure in eyes with any other Schiotz value shows a strong tendency towards the mean i e the applanation pressures tend to be lower than predicted by the calibration scale in eyes with comparatively high

Schiötz pressures and vice versa In consideration of such effects specially designed regression curves might be preferable for prediction of intraocular pressure provided that the dependent variable material and methods of examination used in their preparation have been adequately chosen Anderson & Grant (1970) have given such values to be used for clinical tonography The present study could by no means have been used for that purpose In fact we *could not imagine any use for a simple regression curve of this kind based on* our data A multiple regression analysis of the present material will be published shortly

In order to determine the degree of certainty with which eyes having a given applanation pressure are detected by Schiötz tonometry a description of the variations in distribution of Schiotz readings with applanation pressure was needed For this reason Fig 3 was devised This Figure illustrates that the tendency towards the mean and the wide dispersion of Schiötz values in eyes with identical Goldmann values have additive effects with the result that eyes with borderline applanation pressures (20 5 mmHg) cannot be expected to be identified with an acceptable degree of certainty unless eyes with Schiotz *readings as high as 8 0/7 5 – that is about every second eye – are applanated*

Appreciation of the inaccuracy of Schiötz tonometers has led to general agreement that positive Schiotz readings should be verified by applanation tonometry Such a practice effectively reveals false positives – that is individuals with normal" applanation pressures in spite of low Schiötz readings – but persons with Schiotz readings higher than the generally accepted limit (6 0/7 5) remain unexplored In our material seven out of 24 persons with high applanation pressures (> 20 5 mmHg) would have been missed in that manner

Persons with Schiötz readings just over the limit are much more numerous than are those with high applanation readings The false negatives therefore constitute a much smaller part of the former group than of the latter group and *the possibilities of reducing* the number of false negatives by extending applanation tonometry to people with higher Schiotz readings are limited by a rapidly increasing number of false positives It was concluded that Schiotz tonometry even when supplemented by Goldmann tonometry inevitably fails to detect persons *with moderately increased applanation pressures* to such an extent that its usefulness for glaucoma screening and routine tonometry should be seriously doubted

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ELASTIC PROPERTIES OF INTRAOCULAR BLOOD VESSELS

BY

MILTON BEST* and MICHAEL BLUMENTHAL+

The pressure flow relationship of the intraocular vascular bed was determined by direct perfusion of the ophthalmic artery in enucleated cat eyes From the data obtained pressure resistance pressure radius and tension radius diagrams were constructed for the resistance vessels of the intraocular vascular bed The results indicated that these vessels do not obey Hooke s law in that Young s modulus of elasticity increases as the radius of the vessel is increased The shape of the elastic diagram is not affected by alterations in intraocular pressure or vasomotor tone The addition of levarterenol bitartrate to the perfusate increases critical closing pressure and resistance but decreases circumferential tension in the vessel wall by causing a marked reduction in the radius of the vessel

Key words ocular blood flow – blood vessel elasticity – critical closure – vasomotor tone – intraocular pressure – transmural pressure – ophthalmic artery perfusion

Although the pressure volume relationship of the eye depends on its elastic properties there is scant information available concerning the stress strain relationships of the individual tunics that comprise the ocular coat Studies on

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the extensibility of scleral and corneal strips have been performed (Gloster Perkins & Pommier 1951) and it has been shown that alterations in vascular perfusion pressure to the eye significantly affect the elastic properties of these ocular tissues probably by altering ocular blood volume (Blumenthal Best & Galin 1971 Eisenlohr & Langham 1962) Since changes in ocular blood volume under various conditions are related to the elastic behavior of intra ocular blood vessels it is important to study the elastic properties of these vessels (Best Pola & Galin 1969 Duke Elder 1961 Ytteborg 1960)

From pressure flow relationships of a vascular bed information can be obtained concerning the smaller vessels such as arterioles that offer most of the resistance to flow in the circulation The purpose of the present investiga tion was to determine the pressure flow relationship of the intraocular vascular bed from which typical elastic diagrams of the resistance vessels might be cal culated at different intraocular pressures and under different degrees of vasomotor tone

Material and Method

Ten adult cats weighing between 3 and 5 kg were anesthetized with 25 mg/kg of intravenous sodium pentobarbital and were anticoagulated with 2000 units of heparin sodium They were sacrificed with intravenous sodium pentobar bital both eyes were enucleated and the ophthalmic artery was cannulated with PE 50 polyethylene tubing before its division into the two long *posterior* ciliary arteries (Best Blumenthal Futterman & Galin 1969) A ligature was placed around the end of the optic nerve stump being certain to include the nerve sheaths so that no vessels external to the globe were included in the perfusion The anterior chamber was cannulated with a 23 gauge needle con nected to a reservoir of saline and to a transducer and dynograph *so that the* intraocular pressure could be regulated and recorded

The ophthalmic artery was perfused with room temperature lactated Ringer s *solution* by the vertical tube method (Nichol Girling Jerrard Claxton & Burton 1951) As the experiment progressed the rate of decline of the fluid level in the vertical tube *was* recorded *through* a Statham P23BB pressure transducer located betwen the vertical tube and the ophthalmic *artery* *Fig* 1 *is an* example of such a recording Knowing the cross sectional area of the ver tical tube permitted *the calculation* of pressure flow and pressure resistance curves for the intraocular vascular *bed* *Details* of this technique have been described previously (Best Blumenthal Futterman & Galin 1969)

Since the aim of this investigation was to study the elastic characteristics of intraocular blood vessels at different levels of intraocular pressure it was necessary to obtain pressure flow curves at variable intraocular pressures In order to compare these curves utilizing a common parameter flow was related to the transmural arterial pressure as outlined previously in studies of blood flow in the limb using venous occlusion plethysmography (Burton & Yamada 1951) Perfusion pressure was therefore calculated by subtracting the intra ocular pressure at which flow determinations were made from the level of the fluid in the vertical tube perfusing the ophthalmic artery This method of determining ocular vascular perfusion pressure corresponds to that used in most studies of ocular blood flow (Best Blumenthal Masket & Galin 1970 Bill 1962a b Friedman 1970 Schlegel & Lawrence 1969)

The effect of different levels of intraocular pressure on the pressure flow curve was determined as was the effect of levarterenol bitartrate in concen trations of 5 μg and 15 μg per milliliter in the perfusate

From the pressure flow data resistance to flow was calculated using the formula $R = P/F$ where R is resistance P is perfusion pressure and F is flow Using the Poiseuille formula for resistance the relative changes in radius of the resistance vessels could be deduced since $r \sim 1/R^{\frac{1}{4}}$ where r is the vessel radius The tension in the walls of the resistance vessels was calculated using the law of Laplace $T_c = P_{tm} \times r$ where T_c is circumferential tension and P_{tm} is mean transmural pressure (Burton 1962) Mean transmural pressure in the resistance vessels has been shown to be approximately half the driving pressure (artery minus vein) if most of the resistance is in these vessels (Burton 1962 Folkow & Lofving 1956) In this experiment mean transmural pressure for the intraocular vessels upstream to the effluent veins was considered to be one half the perfusion pressure R r and T_c are expressed in arbitrary units and reflect relative changes in a single equivalent vessel representing the resistance vessels in the intraocular circulation

Results

Fig 1 demonstrates the typical result of a perfusion experiment When intra ocular pressure was kept constant at 26 mmHg the height of perfusate in the vertical tube gradually declined to a level equivalent to 32 mmHg This represents a *critical closing* pressure of 6 mmHg for the intraocular vascular bed (Best Blumenthal Futterman & Galin 1969) Pressure flow data were calculated from this type curve in all further experiments

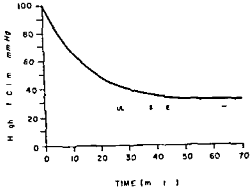


Fig 1

Decline of perfusion column when intraocular pressure is kept constant at 26 mmHg Note that flow through ophthalmic artery ceases when height of perfusing column is 3? mmHg

When flow was plotted against the height of the column perfusing the ophthalmic artery elevation of intraocular pressure from 6 to 40 mmHg was seen to markedly diminish flow (Fig 2) Flow was directly related to the height of the column and ceased in all cases when the column was approximately 6 mmHg above the level of intraocular pressure In order to compare these curves in terms of transmural arterial pressures flow at each intraocular

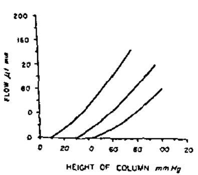


Fig 2

Flow values at different intraocular pressures versus the height of the column perfusing the ophthalmic artery Curves 1 through 3 are at 6 ?5 and 40 mmHg intraocular pressure respectively in an individual eye

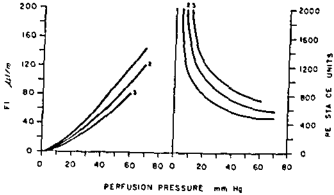


Fig 3

Pressure flow and pressure resistance curves at different levels of intraocular pressure Curves 1 through 3 are at 6 25 and 40 mmHg intraocular pressure respectively in an individual eye Perfusion pressure is the height of the perfusing column minus intraocular pressure

pressure was plotted against the difference between the height of the fluid in the vertical tube perfusing the ophthalmic artery and the intraocular pressure This difference was termed the perfusion pressure and the results are indicated in Fig 3 which shows pressure flow and pressure resistance curves at intraocular pressures of 6 25 and 40 mmHg It should be noted that flow is directly related to perfusion pressure and that at each intraocular pressure the curve shows a slight convexity to the pressure axis As intraocular pressure was increased flow decreased at all perfusion pressures and most

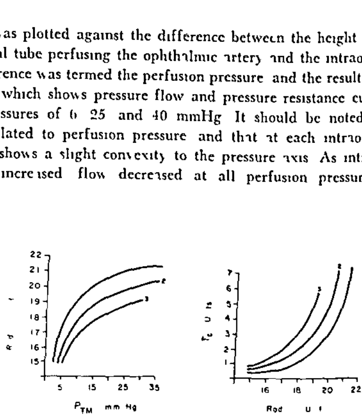


Fig 4

Radius versus transmural pressure and tension versus radius curves for the resistance vessels P_{tm} is transmural pressure T_c is circumferential tension Curves 1 through 3 are at 6 25 and 40 mmHg intraocular pressure respectively in an individual eye

markedly at high perfusion pressures Resistance increased as intraocular pres sure increased

The relationships between radius and transmural pressure and between tension and radius for the resistance vessels were calculated from the pressure resistance curve and are shown in Fig 4 Mean transmural pressure in the resistance vessels is assumed to be half the perfusion pressure (Burton 1962 Fulkow & Iofving 1956) and the radius is expressed in arbitrary units for a single theoretical equivalent vessel giving the resistance The tension radius diagram for that single equivalent vessel is also expressed in arbitrary units The results indicate that at each intraocular pressure the radius of the resist ance vessels is directly but not linearly related to the transmural pressure The tension radius curve at each intraocular pressure also is not linear Tension increases in progressively greater increments as the radius becomes larger

When levarterenol bitartrate was added to the perfusate in concentrations of 5 and 15 μg/ml flow decreased markedly and resistance increased at all perfusion pressures (Fig 5) In addition the critical closing pressure increased in proportion to the concentration of drug The effect of vasomotor tone on the pressure radius and tension radius curve is shown in Fig 6 The addition of levarterenol to the perfusate did not significantly alter the shape of these curves but it markedly decreased the radius of the resistance vessels at all transmural pressures studied

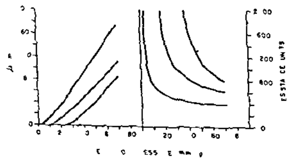


Fig 5

Pressure flow and pressure resistance curves under different degrees of vasomotor tone Curve 1 is without levarterenol curves 2 and 3 are with 5 and 15 μg per milli liter respectively of levarterenol bitartrate in lactated Ringer's solution Intraocular pressure is 95 mmHg for all curves

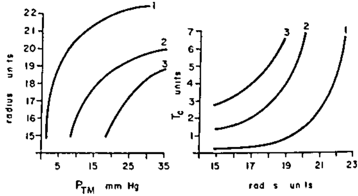


Fig 6

Radius versus transmural pressure and tension versus radius curves for the resistance vessels P_{tm} is transmural pressure T_c is circumferential tension Curve 1 is without levarterenol curves 2 and 3 are with 5 and 15 *ug* per milliliter respectively of levarterenol bitartrate in lactated Ringer s solution Intraocular pressure is 25 mmHg for all curves

Discusison

In studying the elastic behavior of the walls of blood vessels the usual method of constructing an elastic diagram is to plot the changes in circumference as reflected by change in radius and the change in circumferential tension as transmural pressure is increased Elastic diagrams of this nature obtained from this study refer to a theoretical single equivalent vessel that represents those vessels supplying most of the resistance to flow in the intraocular circulation Resistance was calculated from pressure flow diagrams obtained at three levels of intraocular pressure Although at elevated and possibly normal intraocular pressures there is some resistance to flow at the effluent ocular veins (Swann 1954) the data concerning R r P_{tm} and T_c calculated in this study refer to events upstream from the effluent veins Based on observations in previous studies using venous occlusion plethysmography in the limb (Burton & Yamada 1951) it is probable that the intraocular transmural vascular pressures which determine resistance upstream from the effluent veins do not change when intraocular (extravascular) pressure is raised (Burton & Yamada 1951)

The elastic diagrams obtained from this study indicate that in the small vessels of the intraocular circulation resistance to stretch of the vessel wall increases as the wall is stretched This means that Young s modulus of elasticity increases as the radius of the vessel is increased Such elastic behavior of the intraocular vessels is similar to that of the aorta (Nichol 1955) and to

small vessels in other vascular beds with the exception of the kidney (Burton 1962)

In this study the effect of alterations of intraocular pressure on blood flow was measured at a variety of vascular perfusion pressures When flow was plotted against the height of the perfusing column it was noted that elevation of intraocular pressure markedly reduced flow although the critical closing pressure remained constant (Fig 2) This reduction in flow produced by increasing intraocular pressure is due to a decrease in driving pressure (artery to vein) and an increase in resistance Driving pressure is reduced due to the elevation in intraocular venous pressure that occurs secondary to an increase in intraocular pressure (Macri 1964) The distending pressure in the veins however is not altered and remains close to zero In the remainder of the ocular circulation the distending pressure is reduced the largest change occurring in arteries with a smaller change in capillaries This results in an increased vascular resistance

In order to analyze the flow and resistance change at different intraocular pressures in terms of transmural pressures flow at each intraocular pressure was plotted against the effective perfusion pressure which was considered to equal the level of fluid in the vertical tube perfusing the ophthalmic artery minus the intraocular pressure (Fig 3) The results indicate that elevations of intraocular pressure reduce flow and increase vascular resistance at all perfusion pressures the most marked effects occurring at higher perfusion pressures These effects are produced by an apparent reduction in the radius of the resistance vessels at elevated intraocular pressures despite a constant transmural pressure (Fig 4) From this relationship it appears that under conditions of constant vasomotor tone the radius of the resistance vessels in the intraocular vascular bed can be affected by the level of intraocular pressure even though the transmural pressure across the vessel wall is not altered

This analysis of the effect of changes of intraocular pressure on lumenal diameter indicates that at a given transmural pressure the tension in the wall of the resistance vessels will decrease as intraocular pressure increases This is shown in Fig 4 which depicts the relationship between circumferential tension in the vessel wall and transmural pressure at the three intraocular pressures studied Significant decreases in tension in the vessel wall occur after elevations of intraocular pressure at a given transmural pressure This is apparently true at higher transmural pressures

An increase in vasomotor tone by the addition of levarterenol bitartrate to the perfusate caused a marked reduction in radius at all transmural pressures and this accounts for the observed reduction in flow and circumferential tension The marked effect of levarterenol on vasomotor tone was indicated by

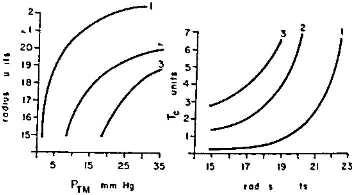


Fig 6

Radius versus transmural pressure and tension versus radius curves for the resistance vessels P_{tm} is transmural pressure T_c is circumferential tension Curve 1 is without levarterenol curves 2 and 3 are with 5 and 15 *ug* per milliliter respectively of levarterenol bitartrate in lactated Ringer's solution Intraocular pressure is 25 mmHg for all curves

Discusison

In studying the elastic behavior of the walls of blood vessels the usual method of constructing an elastic diagram is to plot the changes in circumference as reflected by change in radius and the change in circumferential tension as transmural pressure is increased Elastic diagrams of this nature obtained from this study refer to a theoretical single equivalent vessel that represents those vessels supplying most of the resistance to flow in the intraocular circulation Resistance was calculated from pressure flow diagrams obtained at three levels of intraocular pressure Although at elevated and possibly normal intraocular pressures there is some resistance to flow at the effluent ocular veins (Swann 1954) the data concerning R r P_{tm} and T_c calculated in this study refer to events upstream from the effluent veins Based on observations in previous studies using venous occlusion plethysmography in the limb (Burton & Yamada 1951) it is probable that the intraocular transmural vascular pressures which determine resistance upstream from the effluent veins do not change when intraocular (extravascular) pressure is raised (Burton & Yamada 1951)

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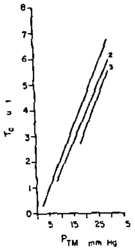


Fig 8
Tension versus transmural pressure curves under different degrees of vasomotor tone Curve 1 is without levarterenol curves 2 and 3 are with 5 and 15 μg per milliliter respectively of levarterenol bitartrate in lactated Ringer s solution Intraocular pressure is 25 mmHg for all curves

that the arteries of the choroid and retina behave differently The elastic diagrams of large veins however differ from those found with arteries (Burton 1967) so that the results of this study may not reflect the elastic behavior of intraocular veins

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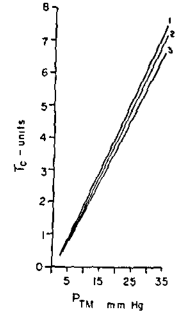


Fig 7

Tension versus transmural pressure curves at different levels of intraocular pressure Curves 1 through 3 are at 6 25 and 40 mmHg intraocular pressure respectively in an individual eye

an increase of 28 mmHg in critical closing pressure that occurred in one eye after the addition of 15 μg/ml to the perfusate Despite the great potency of levarterenol the shape of the elastic diagram is not altered by the large changes in vasomotor tone A given increase in transmural pressure appears to cause a similar increase in vessel radius (Fig 6) or tension (Fig 8) at all degrees of vasomotor tone This finding that the distensibility of intraocular blood vessels is not altered by changes in vasomotor tone is confirmed by other studies of ocular blood vessels (Best Blumenthal & Galin 1970) and is different than the findings for small blood vessels in the systemic circulation where increases in vasomotor tone decrease distensibility (Conrad & Green 1964 Folkow & Lofving 1956)

These observations indicate that the elastic behavior of the resistance vessels of the intraocular vascular bed is similar to that of small blood vessels in other vascular beds except that their distensibility is not altered by changes in vasomotor tone It must be emphasized however that the data of this study refer to a single equivalent vessel that represents the sum total of those vessels supplying most of the resistance to flow in the intraocular circulation Presumably this is the arteriolar bed Larger arteries demonstrate a similar elastic diagram (Nichol 1955 Roach & Burton 1957) and there is no reason to believe

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INTRAOCULAR PRESSURE AND COMMON CAROTID OCCLUSION

BY

MILTON BEST, RAFAEL POLA and MILES A. GALIN

A semilogarithmic relationship has been established between changes in *intraocular pressure* and ocular vascular volume after acute common carotid occlusion. This relationship has been used to derive a *series of* equations that relate the ocular blood volume change after acute common carotid occlusion and the resultant pressure changes in the intraocular vascular compartment by a theoretical constant termed *the coefficient* of vascular rigidity and a variable P_n that reflects the pressure dynamics in the carotid system after acute carotid occlusion. A method for estimating P_n in patients using multiple weight carotid compression tonography is described. P_n was found to vary from normal values in patients with chronic cerebrovascular disease.

Key words: intraocular pressure – carotid occlusion – tonography

A semilogarithmic relationship exists between alterations in intraocular pressure and ocular volume in the living human eye (Friedenwald 1937). Above intraocular pressure of 40–50 mmHg this pressure volume relationship mimics that of the non living eye (Eisenlohr & Langham 1972). Studies from this laboratory have also shown that this semilogarithmic relationship persists when

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Perfusion studies in enucleated cat eyes have established that a semilogarithmic relationship exists between changes in ocular vascular volume and changes in ophthalmic artery perfusion pressure (Best Blumenthal & Galin 1970) The same relationship was found in living cat eyes when acute common carotid occlusion was used to alter ocular vascular perfusion pressure (Best Rabinovitz Pola & Masket 1971) This vascular pressure volume relationship may be expressed in a manner similar to Friedenwald s ocular pressure volume relationship

$$\Delta b = \frac{\text{Log } P_1 - \text{Log } P}{V R} \quad (1)$$

where

Δb = ocular blood volume change after acute common carotid occlusion

P_1 and P = vascular perfusion pressures to the eye before and after acute common carotid occlusion respectively

$V R$ = coefficient of vascular rigidity of the theoretical membrane surrounding the vascular compartment

This ophthalmic vascular pressure volume relationship can also be considered in terms of the changes occurring in the vascular compartment itself after acute common carotid occlusion The immediate fall in intraocular pressure after carotid occlusion results from the fact that the ocular vascular compartment is deprived of a significant part of its blood volume (assuming that run off of blood continues) and collapses due to intrinsic retraction of blood essel walls and extrinsic compression by intraocular pressure If the theoretical elastic membrane surrounding the vascular compartment were rigid and non compressible so that no ocular vascular compression occurred immediately after acute common carotid occlusion the average blood pressure in the vascular compartment would be reduced to a level P_c that is lower than intraocular pressure Vascular compression however does occur and at some point during compression the pressure in the vascular compartment approaches or exceeds intraocular pressure since blood flow through the eye continues Consequently a pressure change in the vascular compartment can theoretically be considered to occur from P to a higher value P The value of P is probably equal to or only slightly higher than intraocular pressure as judged by direct cannulation measurements of iris artery pressure in the rabbit after acute carotid occlusion (unpublished data) By substituting these values in equation (1) additional points in the curve represented by equation (1) are obtained The ocular vascular pressure volume relationship may then be expressed as

$$\Delta b = \frac{\text{Log } P_x \quad \text{Log } P}{V R} \quad (2)$$

where

the technique for altering ocular volume is by acute common carotid occlusion (Best Pola & Galin 1969)

Though it has been reported that blood vessels per se do not enter significantly into intraocular pressure ocular blood volume considerations (Ytteborg 1960) this has not been investigated adequately The present study was designed to consider the significance of the vessels themselves in the relationship between intraocular pressure change and ocular blood volume change as induced by acute common carotid occlusion

Materials and Methods

THEORETICAL CONSIDERATIONS

The force that distends the ocular blood vessels is the blood pressure therein This force is opposed by the tension of the vessel walls and the intraocular pressure (or tissue pressure) The pressure difference across the vessel walls is the transmural pressure and factors that lower transmural pressure will tend to reduce the vessel lumenal diameter After acute common carotid occlusion in the rabbit the transmural pressure in the intraocular vascular compartment is reduced and vascular compression occurs The extent of vascular compression depends in part on the rigidity of the vessel walls The magnitude of vascular compression determines the decrease in ocular blood volume after acute *common carotid occlusion*

Ocular blood volume changes after acute common carotid occlusion have been measured by perfusion techniques designed to determine what volume of fluid must enter the globe to prevent the immediate intraocular pressure reduction that occurs with acute common carotid occlusion (Best Pola & Galin 1969 Best Blumenthal Masket & Galin 1970) These experiments have shown that the semilogarithmic relationship between intraocular volume change and intraocular pressure change described by Friedenwald (1937) holds for changes in ocular volume induced by acute common carotid occlusion

In the analyses to follow the intraocular vascular bed is considered as a single and continuous fluid compartment separated from the remainder of the eye by a single membrane with elastic properties After acute common carotid occlusion an immediate fall in intravascular pressure occurs within this vascular compartment *resulting in vascular compression The amount of compression* that occurs is determined by the change in transmural pressure induced by acute carotid occlusion and by the elastic properties of the membrane surrounding the vascular compartment

Perfusion studies in enucleated cat eyes have established that a semilogarithmic relationship exists between changes in ocular vascular volume and changes in ophthalmic artery perfusion pressure (Best Blumenthal & Galin 1970) The same relationship was found in living cat eyes when acute common carotid occlusion was used to alter ocular vascular perfusion pressure (Best Rabinovitz Pola & Masket 1971) This vascular pressure volume relationship may be expressed in a manner similar to Friedenwald s ocular pressure volume relationship

$$\Delta b = \frac{\text{Log } P_1 - \text{Log } P}{V R} \tag{1}$$

where

Δb = ocular blood volume change after acute common carotid occlusion

P_1 and P = vascular perfusion pressures to the eye before and after acute common carotid occlusion respectively

$V R$ = coefficient of vascular rigidity of the theoretical membrane surrounding the vascular compartment

This ophthalmic vascular pressure volume relationship can also be considered in terms of the changes occurring in the vascular compartment itself after acute common carotid occlusion The immediate fall in intraocular pressure after carotid occlusion results from the fact that the ocular vascular compartment is deprived of a significant part of its blood volume (assuming that run off of blood continues) and collapses due to intrinsic retraction of blood vessel walls and extrinsic compression by intraocular pressure If the theoretical elastic membrane surrounding the vascular compartment were rigid and non compressible so that no ocular vascular compression occurred immediately after acute common carotid occlusion the average blood pressure in the vascular compartment would be reduced to a level P that is lower than intraocular pressure Vascular compression however does occur and at some point during compression the pressure in the vascular compartment approaches or exceeds intraocular pressure since blood flow through the eye continues Consequently a pressure change in the vascular compartment can theoretically be considered to occur from P to a higher value P_x The value of P_x is probably equal to or only slightly higher than intraocular pressure as judged by direct cannulation measurements of iris artery pressure in the rabbit after acute carotid occlusion (unpublished data) By substituting these values in equation (1) additional points in the curve represented by equation (1) are obtained The ocular vascular pressure volume relationship may then be expressed as

$$\Delta b = \frac{\text{Log } P - \text{Log } P}{V R} \tag{2}$$

where

the technique for altering ocular volume is by acute common carotid occlusion (Best, Pola, & Galin, 1969).

Though it has been reported that blood vessels per se do not enter significantly into intraocular pressure ocular blood volume considerations (Ytteborg, 1960), this has not been investigated adequately. The present study was designed to consider the significance of the vessels themselves in the relationship between intraocular pressure change and ocular blood volume change as induced by acute common carotid occlusion.

Materials and Methods

THEORETICAL CONSIDERATIONS

The force that distends the ocular blood vessels is the blood pressure therein. This force is opposed by the tension of the vessel walls and the intraocular pressure (or tissue pressure). The pressure difference across the vessel walls is the transmural pressure, and factors that lower transmural pressure will tend to reduce the vessel lumenal diameter. After acute common carotid occlusion in the rabbit, the transmural pressure in the intraocular vascular compartment is reduced and vascular compression occurs. The extent of vascular compression depends, in part, on the rigidity of the vessel walls. The magnitude of vascular compression determines the decrease in ocular blood volume after acute common carotid occlusion.

Ocular blood volume changes after acute common carotid occlusion have been measured by perfusion techniques designed to determine what volume of fluid must enter the globe to prevent the immediate intraocular pressure reduction that occurs with acute common carotid occlusion (Best, Pola, & Galin, 1969; Best, Blumenthal, Masket, & Galin, 1970). These experiments have shown that the semilogarithmic relationship between intraocular volume change and intraocular pressure change described by Friedenwald (1937) holds for changes in ocular volume induced by acute common carotid occlusion.

In the analyses to follow, the intraocular vascular bed is considered as a single and continuous fluid compartment separated from the remainder of the eye by a single membrane with elastic properties. After acute common carotid occlusion an immediate fall in intravascular pressure occurs within this vascular compartment, resulting in vascular compression. The amount of compression that occurs is determined by the change in transmural pressure induced by acute carotid occlusion and by the elastic properties of the membrane surrounding the vascular compartment.

Perfusion studies in enucleated cat eyes have established that a semilogarithmic relationship exists between changes in ocular vascular volume and changes in ophthalmic artery perfusion pressure (Best Blumenthal & Galin 1970) The same relationship was found in living cat eyes when acute common carotid occlusion was used to alter ocular vascular perfusion pressure (Best Rabinovitz Pola & Masket 1971) This vascular pressure volume relationship may be expressed in a manner similar to Friedenwald s ocular pressure volume relationship

$$\Delta b = \frac{\text{Log } P_1 - \text{Log } P}{V R} \qquad (1)$$

where

Δb = ocular blood volume change after acute common carotid occlusion

P_1 and P = vascular perfusion pressures to the eye before and after acute common carotid occlusion respectively

V R = coefficient of vascular rigidity of the theoretical membrane surrounding the vascular compartment

This ophthalmic vascular pressure volume relationship can also be considered in terms of the changes occurring in the vascular compartment itself after acute common carotid occlusion The immediate fall in intraocular pressure after carotid occlusion results from the fact that the ocular vascular compartment is deprived of a significant part of its blood volume (assuming that run off of blood continues) and collapses due to intrinsic retraction of blood vessel walls and extrinsic compression by intraocular pressure If the theoretical elastic membrane surrounding the vascular compartment were rigid and noncompressible so that no ocular vascular compression occurred immediately after acute common carotid occlusion the average blood pressure in the vascular compartment would be reduced to a level P that is lower than intraocular pressure Vascular compression however does occur and at some point during compression the pressure in the vascular compartment approaches or exceeds intraocular pressure since blood flow through the eye *continues* Consequently a pressure change in the vascular compartment can theoretically be *considered* to occur from P to a higher value P The value of P *is* probably equal to or only slightly higher than intraocular pressure as judged by direct cannulation measurements of iris artery *pressure* in the rabbit after acute carotid occlusion (unpublished data) By substituting these values in equation (1) additional points in the curve represented by equation (1) are obtained The ocular vascular pressure volume relationship may then be expressed as

$$\Delta b = \frac{\text{Log } P - \text{Log } P}{V R} \qquad (2)$$

where

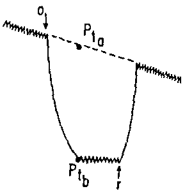


Fig. 1

Schematic representation of the tonographic curve obtained during acute common carotid occlusion. P_{t_b} *is interpolated at a time corresponding to* P_t *in order to eliminate aqueous outflow due to the tonographic effect as a factor in the calculation of volume change after carotid occlusion. O: common carotid occlusion. r: release of common carotid.*

P_x = pressure level in the vascular compartment after acute common carotid occlusion and after vascular compression has occurred. (P_x approximates intraocular pressure after carotid occlusion and with tonometry is equal to P_{t_1} as shown in Fig. 1)

P_{co} = theoretical pressure level in the vascular compartment immediately after acute common carotid occlusion if vascular compression did not occur.

The coefficient of vascular rigidity relates the pressure and volume change within the vascular compartment after acute common carotid occlusion. Perfusion experiments in enucleated and living cat eyes have demonstrated that this coefficient is constant at intraocular pressures between 10 and 40 mmHg and is not altered by inducing varying degrees of vasomotor tone (Best, Blumenthal & Galin, 1970; Best, Rabinovitz, Pola & Masket, 1971).

P_{co} represents the theoretical level to which pressure in the intraocular vascular compartment would fall after acute common carotid occlusion if the vascular membrane were rigid and the vascular compartment could not decrease in size. This pressure level is directly related to the amount that ophthalmic and ciliary artery blood pressure declines after homolateral common carotid occlusion.

P_x, the final pressure level in the vascular compartment after acute carotid occlusion resulting from vascular compression, is approximately equal to or slightly higher than intraocular pressure at intraocular pressures above 20 mmHg. This conclusion was derived from experiments in rabbits and cats in

which iris artery pressure was measured by direct cannulation at various intra ocular pressures after carotid occlusion (unpublished data) In tonometric ex periments therefore P_x can be considered to equal P_{tb} (Fig 1) The validity of using P_{tb} measurements after acute carotid occlusion to calculate the coef ficient of vascular rigidity in humans is based on data from tonometric and direct perfusion techniques in cats which showed that both methods yielded comparable results (Best Masket & Rabinovitz 1971)

Figure 1 is a schematic representation of the tonographic curve obtained during acute common carotid occlusion Points on the curve of intraocular pressure change are represented by P_t and P_{t_b} where P_{t_b} is the intraocular pressure established when vascular compression is complete The blood volume reduction, Δb which occurs after acute common carotid occlusion is measured by the intraocular pressure fall and equals the corneoscleral volume change reflected by the tonometer This volume change includes two factors namely the net decrease in scleral distension from the tonographic resting state and the increase in corneal indentation The decrease in scleral distension is ex pressed by

$$\Delta V_s = \frac{\text{Log } P_t - \text{Log } P_{t_b}}{SR}$$

where

ΔV_s = change in scleral distension

P_t = interpolated intraocular pressure with tonometer on eye prior to caro tid occlusion

P_{t_b} = intraocular pressure with tonometer on eye during occlusion when equilibrium (vascular compression) is established

SR = rigidity of the eye during carotid occlusion

This equation is simply Friedenwald s formula relating intraocular pressure and volume change ($\log \frac{P}{I} = K_v$) using the intraocular pressure change induced by acute common carotid occlusion as one of the points

By considering the intraocular pressure changes after carotid occlusion in terms of I rather than P_t values the increase in corneal indentation can be mathematically eliminated and the decrease in scleral distension can be ex pressed as

$$\Delta V = \frac{\text{Log } I - \text{Log } P_b}{SR}$$

where P and P_b are the intraocular pressures that correspond to P_t and P_{tb} respectively during carotid occlusion

The decrease in scleral distension after acute common carotid occlusion is a result of the intravascular blood volume reduction and therefore $\Delta V = \Delta b$ Consequently equation (2) may be written as

$$\Delta b = \frac{\text{Log } P_{o_a} - \text{Log } P_{o_1}}{S R} \tag{3}$$

For clinical application equation (2) can be written using tonometric values

$$\Delta b = \frac{\text{Log } P_{t_b} - \text{Log } P_{e_o}}{V R} \tag{4}$$

Since the blood volume change is equal to the corneoscleral volume change equations (3) and (4) are equal After transposing the resultant equation is

$$\text{Log } P_{e_1} = \text{Log } P_{t_b} - \frac{V R}{S R} \text{Log } \frac{P_a}{P_{o_b}} \tag{5}$$

Vascular rigidity may be estimated by measuring the ocular blood volume changes after carotid occlusion at two different intraocular pressure levels between 20 and 40 mmHg similarly to techniques used to measure ocular rigidity (Best Masket & Rabinovitz 1971) This is done tonographically by measuring the intraocular pressure change after carotid occlusion using two plunger weights (5 5 and 10 0 g) Animal studies indicate that this method of estimating vascular rigidity is valid at various levels of arterial perfusion pressure to the eye as long as the perfusion pressure remains above the critical closing value of the ocular vascular bed after acute common carotid occlusion (Best Rabinovitz Pola & Masket 1971) Systemic blood pressure therefore should play a very small role if any in the determination of vascular rigidity Measurement of vascular rigidity in normal humans does confirm this (Best Masket & Rabinovitz 1971)

The equations to calculate the coefficient of vascular rigidity then are

$$\Delta b = \frac{\text{Log } P_{o} - \text{Log } P_{1}}{S R}$$

$$\Delta b = \frac{\text{Log } P_{a} - \text{Log } P_{1}}{S R}$$

$$V R = \frac{\text{Log } P_{t_b} - \text{Log } P_{t_1}}{\Delta b - \Delta b} \tag{6}$$

where

Δb = blood volume change after carotid occlusion measured with a 5 5 g weight

jb = blood volume change after carotid occlusion measured with a 10 0 g weight

Equation (5) can be used to approximate the pressure in the vascular compartment of the eye immediately after acute common carotid occlusion assuming intraocular vascular compression did not occur Although this is a theoretical value it is still of significance since it may be used to infer the pressure dynamics in the carotid system after acute occlusion This equation forms the basis of the clinical studies described below

CLINICAL STUDIES

Patients with and without chronic cerebrovascular disease and varying in age from 18 to 83 years were selected for this study Detailed ocular examination was performed in each patient and those with corneal or scleral disease were eliminated from the study In addition patients with advanced arteriosclerotic disease of the retina or evidence of previous retinal vascular occlusion were not included

The technique of common carotid compression tonography has been outlined elsewhere (Galin Dodick & Best 1967 Galin Rodriguez Barrios Pola & McLean 196) Patients were studied initially to determine whether compression at different carotid levels would result in differences in the form or amplitude of the tonographic tracing In all instances however care was exercised to avoid the carotid sinus In all other aspects of the study carotid compression was always performed as low in the neck as possible Tonographi recordings were obtained for each patient using the 5 5 and 10 0 g weights with compression always applied to the common carotid artery at the same point The electrocardiogram or the radial pulse was monitored in each patient Tonographic recordings were obtained with the Crescent electronic tonometer (-1 to 70 scale) connected to the Crescent recorder (speed 4 inches/min) or to the Speedomax H recorder (speed 2 inches/min)

Calculations of volume changes after acute common carotid compression were made from the tonographic records utilizing Friedenwald's tables in nomogram form Ocular rigidity (S R) was calculated by comparing intraocular pressure measurements by applanation and Schiotz tonometry without compensation for positional differences P and V R were calculated using equations (5) and (6) respectively An alternate graphic method for estimating V R and I is shown in Fig 2 The first step is to calculate the volume change from I_t to I_{t_b} (intraocular pressures before and after carotid occlusion respectively with the tonometer on the eye) using the tonographic records ob

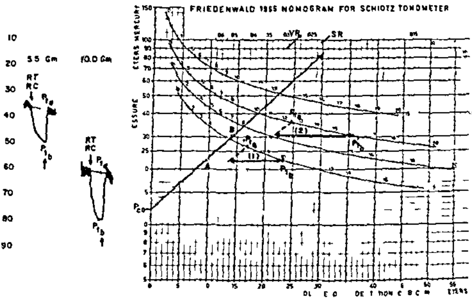


Fig. 2

Graphic method for estimating V.R. and P_{co}. See text for explanation. RT: right tonography; RC: right carotid compression; V.R.: vascular rigidity; S.R.: scleral rigidity. Scale: –1 to 20.

tained with the 5.5 g plunger weight. This volume change is then plotted against the intraocular pressure corresponding to P_{t_b} (point A in Fig. 2). The same type of calculation is then made from the tonographic record obtained with the 10.0 g weight and the volume change is plotted at an intraocular pressure corresponding to P_{t_b} (point B in Fig. 2). Points A and B are connected with a straight line. A line drawn parallel to this and passing through 20 mmHg on the ordinate will cross through a value at the top of the nomogram indicating the vascular rigidity. The point where the line connecting points A and B crosses the ordinate indicates P since at this level of intraocular pressure there would be no volume change in the eye during acute common carotid compression.

Results

In general, compression of the common carotid artery at different levels in the neck but inferior to the carotid sinus resulted in similar curves without change in the radial pulse or electrocardiogram. It is sufficient to monitor the patient's cardiovascular response to compression solely by the radial pulse, which can

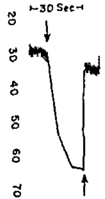


Fig 3
Normal tonographic curve There is a rapid fall upon compression and a virtually perpendicular rise upon release of the carotid artery ↓ compression of carotid artery ↑ release of carotid artery

easily be done by the same individual applying carotid compression By this technique the rare occurrence of bradycardia can be detected immediately The homolateral temporal artery may be palpated to be sure that the compressed carotid artery is completely occluded

Figure 3 demonstrates a curve with a typically normal contour There is a rapid fall in intraocular pressure on compression and a virtual perpendicular rise upon release of the common carotid artery The intraocular pressure either

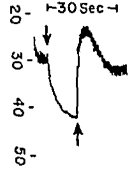


Fig 4
Intraocular pressure may recover to a level above the tonographic baseline for a short period of time after release of the carotid artery ↓ compression of carotid artery ↑ release of carotid artery

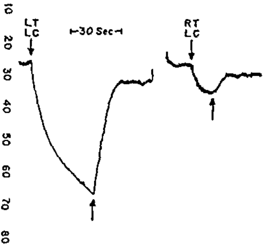


Fig 5

Tonographic curves due to a carotid sinus reflex There is a rapid fall upon compression but the recovery upon release of the carotid artery is slower than normal Bradycardia is apparent upon cross compression (RT LC) and gives rise to the false impression that cross circulation exists LT left tonography LC left carotid compression RT right tonography ↓ compression of carotid artery ↑ release of carotid artery

reaches or exceeds the tonographic baseline for a short period of time (Fig 4) This curve is readily distinguishable from the type of curve due to a sinus reflex (Fig 5) In the latter intraocular pressure may continue to fall after

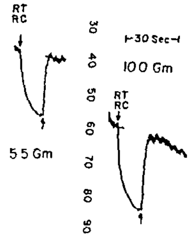


Fig 6

Normal tonographic records using the 5 5 g and 10 0 g plunger weights showing intraocular pressure changes in the right eye after acute homolateral common carotid compression Scale −1 to 20

Table I

Ocular rigidity (S.R.) vascular rigidity (V.R.) and P_{co} in normal patients. For each patient upper and lower values represent right and left eye respectively

Patient	S.R.	V.R.	P_o
1	0.020	0.021	13
	0.021	0.022	13
2	0.026	0.024	7
	0.026	0.022	8
3	0.026	0.026	14
	0.024	0.025	10
4	0.024	0.026	10
	0.019	0.026	10
5	0.024	0.024	11
	0.022	0.021	11
6	0.019	0.021	11
	0.018	0.020	11
7	0.023	0.020	13
	0.02[illegible]	0.020	11
8	0.034	0.027	12
	0.029	0.0[illegible]9	11
9	0.022	0.022	10
	0.033	0.017	12
10	0.026	0.0[illegible]2	12
	0.029	0.021	14
11	0.027	0.017	13
	0.05[illegible]	0.0[illegible]3	13
12	0.0[illegible]	0.023	15
	0.0[illegible]	0.032	14
13	0.026	0.0[illegible]7	16
	0.027	0.021	16
14	0.0[illegible]	0.02[illegible]	17
	0.023	0.025	17
15	0.026	0.030	15
	0.0[illegible]6	0.030	14

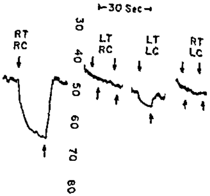


Fig 7

Carotid compression tonography curves using the 5 5 g plunger weight showing that the fall in intraocular pressure in the right eye (RT RC) is normal and in the left eye (LT LC) is markedly reduced

release of carotid compression In addition there is a slow return to normal intraocular pressure after release of compression and bradycardia may be apparent in the tonographic tracing The sinus reflex may give a false impression that cross circulation exists

Fifteen patients (30 eyes) ranging in age from 18 to 67 years and without apparent cerebrovascular disease were studied Figure 6 represents the type of carotid compression tonographic curves obtained with 5 5 and 10 0 g

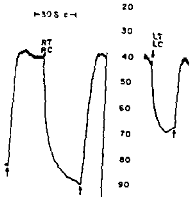


Fig 8

Carotid compression tonography curves using the 5 5 g plunger weight showing a very large fall in intraocular pressure especially in the right eye RT right tonography RC right carotid compression LT left tonography LC left carotid compression

Table II

Ocular rigidity (S R) vascular rigidity (V R) and P_{co} in patients with chronic cerebrovascular disease in whom carotid compression tonography revealed small falls in intraocular pressure

Patient	S R.	V R	P_o
1	0.076	0.027	17
2	0.019	0.037	20
3	0.026	0.038	21
4	0.020	0.045	21
5	0.023	0.049	22
6	0.025	0.052	23
7	0.021	0.059	25

weights Table I lists the ocular rigidity vascular rigidity and P_{co} values obtained in these patients The mean values and standard deviations were 0.0?4? ± 0.0038 for ocular rigidity 0.0236 ± 0.0037 for vascular rigidity and 1? ± 2.5 mmHg for P_o P was calculated using equation (5) and the data obtained from the tonographic curve with the 5.5 g weight

In the patients with chronic cerebrovascular disease that were studied two types of abnormal carotid compression tonographic curves were obtained The more frequent type was found in seven patients and is illustrated in Fig 7 in which the fall in intraocular pressure after homolateral common carotid compression is normal in the right eye and markedly reduced in the left eye Figure 8 demonstrates the second type of abnormal curve that was found in three patients and is characterized by a very large fall in intraocular pressure

Table III

Ocular rigidity (S R) vascular rigidity (V R) and P_c in patients with chronic cerebrovascular disease in whom carotid compression tonography revealed abnormally large falls in intraocular pressure

Patient	S R	V R	P_c
1	0.0?4	0.019	[illegible]
2	0.021	0.037	5
3	0.029	0.026	3

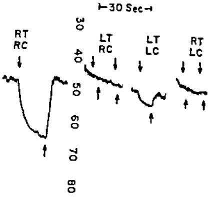


Fig 7

Carotid compression tonography curves using the 5 5 g plunger weight showing that the fall in intraocular pressure in the right eye (RT RC) is normal and in the left eye (LT LC) is markedly reduced

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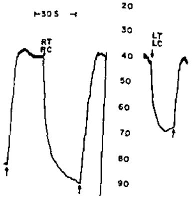


Fig 9

Carotid compression tonography curves using the 5 5 g plunger weight showing a very large fall in intraocular pressure especially in the right eye RT right tonography RC right carotid compression LT left tonography LC left carotid compression

Table II
Ocular rigidity (S R) vascular rigidity (V R) and P_e in patients with chronic cerebrovascular disease in whom carotid compression tonography revealed small falls in intraocular pressure

Patient	S R	V R	P_o
1	0 0[illegible]6	0 027	17
2	0 019	0 03[illegible]	20
3	0 0[illegible]6	0 038	21
4	0 0[illegible]0	0 045	[illegible]1
5	0 0[illegible]3	0 049	22
6	0 025	0 0[illegible]2	23
7	0 021	0 0[illegible]9	25

weights Table I lists the ocular rigidity vascular rigidity and P_{eo} values obtained in these patients The mean values and standard deviations were 0 0[illegible]47 ± 0 0038 for ocular rigidity 0 0236 ± 0 0037 for vascular rigidity and 12 ± 2 5 mmHg for P P_e was calculated using equation (5) and the data obtained from the tonographic curve with the 5 5 g weight

In the patients with chronic cerebrovascular disease that were studied two types of abnormal carotid compression tonographic curves were obtained The more frequent type was found in seven patients and is illustrated in Fig 7 in which the fall in intraocular pressure after homolateral common carotid compression is normal in the right eye and markedly reduced in the left eye Figue 8 demonstrates the second type of abnormal curve that was found in three patients and is characterized by a very large fall in intraocular pressure

Table III
Ocular rigidity (S R) vascular rigidity (V R) and P in patients with chronic cerebrovascular disease in whom carotid compression tonography revealed abnormally large falls in intraocular pressure

Patient	S R	V R	P_e
1	0 0[illegible]4	0 019	7
[illegible]	0 0[illegible]1	0 037	5
3	0 0[illegible]9	0 0[illegible]6	3

after homolateral common carotid compression The values for ocular rigidity vascular rigidity and P_{co} are listed in Table II for the former and in Table III for the latter patients

For values of P_{co} higher than normal (Table II) vascular rigidity was also increased Although a direct relationship appears to exist between vascular rigidity and P_{co} in these patients not enough patients have as yet been studied to justify this conclusion In the patients with abnormally low P_{co} values no constant relationship was found between vascular rigidity and P_{co}

Discussion

There is evidence that blood vessels act like tubes with rigid walls as long as their transmural pressure remains significantly higher than their critical closing pressure (Nichol Girling Jerrard Claxton & Burton 1951) As the critical closing pressure is approached however there is a sudden dramatic increase in vascular resistance and a decrease in flow which indicates an instability of the vessel wall in the vicinity of the critical closing pressure (Best Blumenthal Futterman & Galin 1969) In the rabbit and cat eye it would appear that for intraocular pressures between 20 and 40 mmHg the vascular transmural pressure is high enough to exceed the critical closing pressure during acute occlusion of the common carotid artery (Best Blumenthal Futterman & Galin 1969 Best Blumenthal Masket & Galin 1970 Best Blumenthal & Galin 1970 Best Rabinovitz Pola & Masket 1971) Within this range then the concept of a coefficient of vascular rigidity applies and it has been measured experimentally in enucleated and living cat eyes (Best Blumenthal & Galin 1970 Best Rabinovitz Pola & Masket 1971) In the present study vascular rigidity is a coefficient that correlates the volume of vascular compression resulting from acute common carotid occlusion with the change in pressure in the intraocular vascular compartment from P to P_{t_b} P_e is the immediate intravascular pressure after common carotid occlusion and P_{t_b} calculated with the tonometer on the eye is the resulting intraocular pressure after vascular compression has occurred

It seems fair to assume that if the carotid artery is significantly stenotic the fall in pressure in the ocular intravascular compartment during homolateral carotid compression is less than when the carotid is fully patent especially if collateral circulation has developed The vascular volume change within the eye therefore will also be smaller in the presence of carotid stenosis as has

been demonstrated in animals in this laboratory by perfusion experiments (Rabinovitz & Best 1972) Smaller intraocular volume changes during homo lateral carotid compression in a case of carotid stenosis or occlusion therefore reflect the greater than anticipated residual pressure in the vascular compart ment due to collateralization or a higher than normal vascular rigidity The theoretical V R can be calculated directly but P_{co} is measurable only indirectly

This study demonstrates that in subjects with apparently normal cerebro vascular circulations P_o is approximately 12 mmHg and the mean value for V R is 0 0?36 Elevated values of P_{co} were found in patients with chronic cerebrovascular disease and there appeared to be a direct relationship between P_{co} and V R Abnormally low values of P_{co} were found in three patients with chronic cerebrovascular disease in whom it was noted that the fall in intra ocular pressure was larger than average during common carotid compression This may be the result of a very large fall in intravascular pressure If the *resulting* intravascular pressure approached the critical closing value for some intraocular vessels an unstable vascular state would result Small differences in the amount of closure or time of closure of intraocular vessels would then result in significant differences in the volume calculated with the 5 5 and 10 0 g weights The calculation of V R would therefore be *inaccurate in this* situation

It is probable that the pressure fall in the ocular vascular compartment and the carotid artery after acute carotid occlusion are directly related The per centage fall of pressure in the central retinal artery and the carotid artery after occlusion are similar (Tindall Dukes Cupp & Noble 1960) In fact after oc clusion of the common carotid artery the percentage drop in pressure is the same in the internal carotid and its branches including vessels as small as 0 4 mm in diameter (Bakay & Sweet 1959)

The common carotid compression tonography test is of value in diagnosing the presence of carotid occlusion and the nature of collateral flow to the eye from the contralateral carotid artery (Galin Dodick & Best 1967 Galin Rodriquez Barrios Pola & McLean 1967) The present study describes a quantitative technique with which it may be possible to assess the *residual* vascular *pressure in* various degrees of carotid stenosis and the degree of collateral *circulation* This evaluation is based on estimating P_{co} Theoretically high values of P_c might be found in carotid stenosis and low values would reflect a lack of potential collateral blood supply to the eye being tested during acute common carotid compression A study is presently underway to assess these considerations in patients with angiographically demonstrated carotid occlusion as well as to determine the significance of V R in various disorders known to be associated with arteriosclerotic vascular disease

Acknowledgments

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fusion tests Barany (1954) demonstrated that the outflow resistance in cattle eyes could be decreased over 50 % with intracameral perfusion of testicular hyaluronidase Further perfusion tests using various kinds of hyaluronidase seemed to confirm that the affected mucopolysaccharide layer in the trabecular meshwork was hyaluronic acid or a closely related mucopolysaccharide (Barany 1956)

Although Meyer (1947) stated that approximately 95 % of aqueous hyaluronic acid in cattle eyes was depolymerized by hyaluronidase in the aqueous no change in intraocular pressure has been found after feeding animals hyaluronidase inhibitors (Barany 1954) (In the above study the level of hyaluronic acid was not measured – only facility of outflow) No confirmation of any discernible amount of hyaluronidase has been made using various turbidimetric bacteriological and viscosimetric techniques (Barany & Woodin 1955 Mayer et al 1956 Langley & McCullock 1958)

Using Barany s perfusion technique with hyaluronidase François et al (1956b) confirmed that a 40–50 % increase in facility of outflow could be established in rabbit eyes however the effect of hyaluronidase on outflow resistance was much more variable in humans After intracameral India Ink was perfused *in vitro* both pre and post hyaluronidase histological sections of human eyes showed that while perfusion fluid left the anterior chamber through scleral trabeculum Schlemm s canal and the intrascleral plexus no appreciable difference was seen in sections before or after the administration of hyaluronidase Histological examinations of rabbit eyes however showed infiltration of trabeculumn much more pronounced with *in vitro* studies of India ink post hyaluronidase Microradiographic Thiotrast studies showed contrast material more profusely in trabeculum of both rabbit and human eyes after hyaluronidase In concluding their study it was thought that the addition of hyaluronidase to perfusion fluid had a significant and more varied action on outflow resistance in human eyes as compared with rabbit eys Later Thiotrast studies after hyaluronidase also suggested that the orifices of the inner wall of Schlemm s canal in human eyes may be enlarged after exposure to hyaluronidase and that the entire trabecular lamellar meshwork becomes more permeable to Thiotrast (François et al 1956a)

Pedler (1956) and later Lieb & Stark (1966) using a modification of Barány s perfusion technique again confirmed that in cattle eyes an approximate 30–50 % increase in outflow facility could be seen after hyaluronidase In determining outflow resistance Pedler found a mean decrease of approximately 50 % in human eyes after hyaluronidase but stated that results were extremely erratic Lieb found no perceptible change in facility after hyaluronidase in human eyes and related this difference to the different anatomical and histo

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THE EFFECT OF HYALURONIDASE ON THE FACILITY OF OUTFLOW IN NORMAL AND BUPHTHALMIC RABBITS

BY

JAMES L BROWN and WALTER J GEERAETS

This study confirms the results of other investigators that hyaluronidase temporarily increases the facility of outflow most probably by its effect on a hyaluronic acid like substance covering the trabecular meshwork in normal rabbits
In demonstrating that intracameral hyaluronidase had essentially no effect on outflow facility in congenital buphthalmic rabbits one might postulate that these rabbits have either a functionless trabecular meshwork or an overlying mucopolysaccharide layer that is unresponsive to hyaluronidase

Key words aqueous – hyaluronidase – rabbit

Research in the field of glaucoma was stimulated by the detection of a mucopolysaccharide in the trabecular meshwork of the anterior chamber Utilizing various staining techniques this mucopolysacchride was found to be sensitive to hyaluronidase and therefore thought to be hyaluronic acid (Vrabec 1954 Bárany et al 1957 Zimmerman 1957 Berggren & Vrabec 1959) Using per

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hyaluronidase but demonstrated that it was secondary to changes in the corneal curvature rather than to fluctuations in lenticular shape as proposed by Stanworth

Since the influence of hyaluronidase on anterior chamber mechanics in humans and normal rabbits has been established the purpose of this investigation is to determine what effect intracameral hyaluronidase might have on buphthalmic rabbit eyes using normal albino rabbit eyes as controls

Material and Method

The technique utilized in this study was similar to that of Noah et al (1971) In previous investigations it was found that the stabilization of facility of outflow during repeated determinations was dependent on the rabbits being in a constant plane of anesthesia Since the buphthalmic strain of rabbits in our study has proven to be a poorer anesthetic risk than normal albino rabbits various types and combinations of intravenous anesthetic agents were investigated It was found that a combination of Urethane (25% solution) and Sodium Pentobarbital 60 mg/cc proved most satisfactory The femoral vein of each animal was cannulated to provide a route for drug administration

Table II
Effect of Wydase (intracameral) on kC in albino rabbits

No	Eye	Rabbit No	Date	kC	kC'	% Δ kC
1	OD	284	4 6/71	0 0068	0 0119	+ 75 0
2	OD	83	4/ 0 71	0 0087	0 0193	+ 135 0
3	OD	311	5/11/71	0 01	0 0119	— 2 5
4	OD	960	/11/71	0 0108	0 0161	+ 49 0
	OS	330	5 18 71	0 0104	0 0101	— 2 9
6	OD	344	5/18/71	0 0196	0 0178	+ 41 3
	OD	945	5 25/71	0 0193	0 0094	+ 139 0
8	OD	346	5/25 71	0 0106	0 0144	+ 35 8
9	OD	340	6 1/71	0 0115	0 0161	+ 40 0
10	OD	965	6 1/71	0 0178	0 0164	— 7 8
					Average % Δ kC	+ 50 2

Table I

Repeated intracameral saline injections in buphthalmic rabbits

No	Eye	Rabbit	Date	C (before drug)	C (after drug)	% ΔC
1	OD	684760	11/3/70	0 0038	0 0030	−21 0
2	OS	684760	11/10/70	0 0028	0 002[illegible]	− 3 6
3	OS	690[illegible]28	12/1/70	0 0051	0 0054	+ 5 9
4	OD	702430	2/16/71	0 0055	0 0049	− 9 [illegible]
5	OD	702431	2/23/71	0 0089	0 0087	− 2 2
6	OD	702426	3/16/71	0 0082	0 0084	+ [illegible] 4
7	OS	702426	3/16/71	0 0078	0 0120	+54 0
8	OD	701966	3/9/71	0 0097	0 0064	−34 0
9	OD	701744	3/23/71	0 0033	0 0032	− 3 0
10	OS	701744	3/23/71	0 0025	0 0032	+28 0
11	OD	684760	4/6/71	0 0049	0 0039	−20 0
					Average % ΔC	− 0 [illegible]

logical configurations of the cattle and human anterior chamber angle It was not clear however whether the elapsed time between death and the utilization of eyes in their study was the same for cattle and human eyes

Although the effects of hyaluronidase appear to be variable Linn (1950) Vanni & Lepri (1959a) and Rosengren (1961) have shown that injections of hyaluronidase into the anterior chamber subconjunctiva or vitreous can cause transient decrease of intraocular pressure in glaucomatous patients to normal and subnormal levels Landesberg (1959) introduced hyaluronidase by iontophoresis and found 50 % decrease in intraocular pressure in 20 glaucomatous patients after 24 hours Seven of these patients continued to have decreased pressures a week later Unfortunately a longer follow up of the above cases is not given Vanni & Lepri (1959b) also found a distinct decrease in intraocular pressure persisting for 1–3 days in open angle glaucoma patients receiving hyaluronidase via iontophoresis

After giving subconjunctival injections of hyaluronidase to young patients with late congenital glaucoma Stanworth (1966) noted not only a decrease in intraocular pressure but a minus 1–2 diopter refractive change appearing 4–7 days post injection The refractive errors in all cases returned to pre injection determinations within several weeks Treister et al (1969) substantiated this disparity in refractive error after subconjunctival injection of

a Sanborn transducer and amplifier two decay curves were plotted both pre and post saline (control) or hyaluronidase injection To allow the eye to attain a steady state condition an interval of 30 minutes was allowed both after insertion of needles into the anterior chamber and after the injection of Wydase or saline Because of the volume disparity between normal and buphthalmic eyes 0 01 and 0 03 ml of 7 5 I U hyaluronidase/ml (Wydase pH 6 6) respectively was injected into the normal and buphthalmic eyes In comparing anterior chamber activity after the injection of saline and hyaluronidase the results were equivalent i e 0 trace flare in anterior chamber

The average decay values of the two pre injection determinations are compared with the average of the post injection recordings

Results

A statistical evaluation was compounded using the paired t test along with a null hypothesis for 1 % significance giving the probability that hyaluronidase will not affect the kC values in any group of animals tested (kC representing ocular rigidity × facility of outflow) (Noah et al 1971) The fact that the kC values in normal albino rabbits increased by an average of 50 19 % after hyaluronidase coupled with the probability of accepting the null hypothesis $<0 01$ compel one to reject the hypothesis One finds a probability of $>0 05$ in evaluating the results from the buphthalmic animals receiving saline and hyaluronidase injections consequently forcing one to accept the null hypothesis that there is no conclusive evidence of any significant effect on kC in buph thalmic rabbits receiving injections of normal saline or hyaluronidase

Discussion

Lee (1969) in a comparative study of histological and gonioscopic findings in two normal and three buphthalmic rabbit eyes relates the decrease in outflow facility in buphthalmic eyes to a malformation of the filtration angle This consists of abnormal insertion of uveal tissue absence of the Space of Fontana poorly developed trabecular channels and undifferentiated uveal tissue closely adherent to the sclera and filtration angle Considering this information one is not surprised to find that hyaluronidase has a *negligible* effect on the outflow facility in buphthalmic rabbits assuming the mechanism

Table III

Effect of intracameral wydase injection in buphthalmic rabbits

No	Eye	Rabbit No	Date	kC	kC	% ΔkC
1	OD	701877	6/8/71	0 0012	0 0011	− 8.3
2	OD	688478	6/15/71	0 0040	0 0043	+ 7.5
3	OS	702429	6/22/71	0 0075	0 0059	−21.3
4	OD	690226	6/29/71	0 0014	0 0013	− 7.1
5	OS	701877	7/12/71	0 0056	0 0054	− 3.6
6	OD	693113	7/19/71	0 0037	0 0029	−21.6
7	OD	702303	7/26/71	0 0040	0 0036	−10.0
8	OD	688751	7/26/71	0 0052	0 0050	− 3.8
9	OD	701877	8/16/71	0 0021	0 0018	−14.3
					Average % ΔkC	− 9.9

Genotypic buphthalmic rabbits with no clinical evidence of glaucoma (data were not utilized)

No	Eye	Rabbit No	Date	kC	kC	% ΔkC
10	OD	693172	6/22/71	0 0120	0 0163	+ 35.8
11	OD	683906	8/2/71	0 0060	0 0094	+ 56.7
					Average % ΔkC	+ 46.3

Urethane was selected for its prolonged hypnotic and mild analgesic properties and because it produces only minimal respiratory depression compared with morphine and barbiturate derivatives In this 2 5 hour procedure a constant Urethane drip was deemed impractical because of fluid overload and due to the sclerotic nature of the drug a higher concentration could not be used Approximately 20–30 minutes after 1 3–1 5 g/kg injection of Urethane Pentobarbital 10–20 mg/kg was given to increase hypnotic effects and provide greater analgesia By observing depth and rate of respiration and analgesia one could supplement this regimen with 4–8 mg/kg of Pentobarbital IV every 20–30 minutes to keep the average rabbit in a relatively constant plane of anesthesia

Ten normal New Zealand Albino rabbits along with 20 buphthalmic rabbits of the same strain were used With cannulized anterior chamber attached to

a Sanborn transducer and amplifier two decay curves were plotted both pre and post saline (control) or hyaluronidase injection To allow the eye to attain a steady state condition an interval of 30 minutes was allowed both after insertion of needles into the anterior chamber and after the injection of Wydase or saline Because of the volume disparity between normal and buphthalmic eyes 0 01 and 0 03 ml of 7 5 I U hyaluronidase/ml (Wydase pH 6 6) respectively was injected into the normal and buphthalmic eyes In comparing anterior chamber activity after the injection of saline and hyaluronidase the results were equivalent i e 0 trace flare in anterior chamber

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1	OD	701877	6/8/71	0 0012	0 0011	— 8 3
2	OD	683473	6/15/71	0 0040	0 0043	+ 7 5
3	OS	702429	6/22/71	0 0075	0 0059	—21 3
4	OD	690226	6/29/71	0 0014	0 0013	— 7 1
5	OS	701877	7/12/71	0 0056	0 0054	— 3 6
6	OD	693113	7/19/71	0 0037	0 0029	—21 6
7	OD	702303	7/26/71	0 0040	0 0036	—10 0
8	OD	683751	7/26/71	0 0052	0 0050	— 3 8
9	OD	701877	8/16/71	0 0021	0 0018	—14 3
					Average % ΔkC	— 9 9

Genotypic buphthalmic rabbits with no clinical evidence of glaucoma (data were not utilized)

No	Eye	Rabbit No	Date	kC	kC	% ΔkC
10	OD	693172	6/22/71	0 0120	0 0163	+ 35 8
11	OD	683906	8/2/71	0 0060	0 0094	+ 56 7
					Average % ΔkC	+ 46 3

Urethane was selected for its prolonged hypnotic and mild analgesic properties and because it produces only minimal respiratory depression compared with morphine and barbiturate derivatives In this 2 5 hour procedure a constant Urethane drip was deemed impractical because of fluid overload and due to the sclerotic nature of the drug a higher concentration could not be used Approximately 20–30 minutes after 1 3–1 5 g/kg injection of Urethane Pentobarbital 10–20 mg/kg was given to increase hypnotic effects and provide greater analgesia By observing depth and rate of respiration and analgesia one could supplement this regimen with 4–8 mg/kg of Pentobarbital IV every 20–30 minutes to keep the average rabbit in a relatively constant plane of anesthesia

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of increased outflow facility seen in normal rabbits to be a dissolution of a hyaluronic acid like layer coating the normal trabecular meshwork and outflow channel

Although the presence of a mucopolysaccharide substance coating the trabecular meshwork in buphthalmic rabbits was not histochemically proven to exist in this study hyaluronidase did produce a 46% increase in outflow facility in two genotypic glaucomatous rabbits with normal ocular phenotypes These animals were not included in the experimental group because they had no clinical evidence of glaucoma however, it was interesting to observe that hyaluronidase did provoke an increase in outflow facility in these genotypic glaucomatous rabbits This would suggest that a mucopolysaccharide layer responsive to hyaluronidase does exist in some hereditary glaucomatous rabbits and that in others it either becomes unresponsive to hyaluronidase or its response is masked by a markedly abnormal anterior chambe angle

Since Eakins (1969) demonstrated that Pentobarbital caused a greater effect in lowering intraocular pressure than other types of anesthesia including Urethane one should note that animals in this study had both drugs given 30 minutes prior to decay curve evaluations Since these animals had a deep hypnotic effect from the Urethane only minimal amounts of Pentobarbital were needed to provide more analgesia consequently the problem of poorly maintained intraocular pressure alluded to by Eakins using Pentobarbital was not experienced

As in previous studies (Noah et al 1971 Noah & Geeraets 1971) the kC values obtained in this study were derived from decay curve analysis To be accurate one would assume a consistency in aqueous production thus before each decay curve injection was made sufficient time was allowed for the baseline to stabilize This rate of aqueous production was also altered with each injection secondary to an increase in intraocular pressure however the pseudofacility values were not felt to significantly affect the resulting kC values in that the intraocular pressures attained for the two pre injection and post injection curves were essentially equal

Stanworth (1968) stated that he found no change in scleral rigidity following 1500 I U of subconjunctival hyaluronidase in human eyes No significant change in scleral rigidity was found in the present study after 0 075 and 0 225 I U were intracamerally injected in the normal albino and buphthalmic rabbit eyes respectively consequently any change in kC values could be attributed to facility alone

Because of the effect that hyaluronidase has on refractive properties in the human eye also alluded to by Stanworth one will have to analyze this problem carefully in considering the use of hyaluronidase in glaucomatous individuals

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SECONDARY GLAUCOMA CAUSED BY ORBITAL LYMPHANGIOMA

BY

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The present paper is a case report of monocular glaucoma in an 11 year old boy as a consequence of extraocular venous obstruction caused by a retrobulbar neoplasm most probably a lymphangioma The prognosis and therapeutic possibilities are discussed Glaucomas with this pathogenesis are rare and lymphangiomas in the orbit have not previously been reported to cause secondary glaucoma

Key words secondary glaucoma – orbital lymphangioma

The present article describes a case of monocular glaucoma in an 11 year old boy as a consequence of extraocular venous obstruction caused by orbital neoplasm

Secondary glaucoma based on extraocular venous obstruction may be caused by mechanical thrombotic or inflammatory factors In principle the obstruction may be localized either in the vorticous veins the anterior ciliary veins the ophthalmic vein or in the veins of the neck in the last case mainly the jugular vein or the superior cava vein The orbital veins do not possess valves for which reason an increase of pressure at this level will cause a linear and instant increase of the intraocular pressure

Only rather few cases of glaucoma based on orbital tumors are described in the literature Bietti & Vanni in 1960 described six cases of monocular glau

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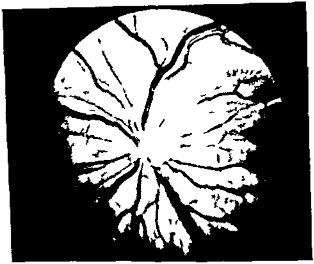


Fig 2
Fundus of the left eye

lined with endothelium They contained protein and scattered lymphocytic cells but no erythrocytes

The patient was admitted to our department in September 1969 for congenital left ptosis Further examination of this eye revealed exophthalmos on the left side and secondary glaucoma Only the ptosis had been noticed by the patient

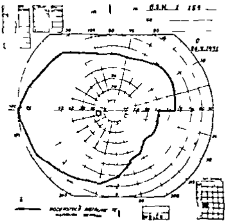


Fig 3

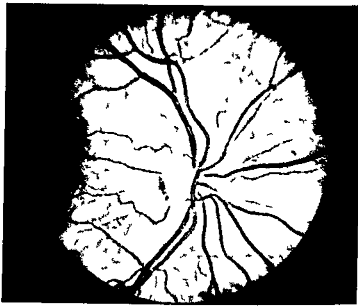


Fig 1
Fundus of the right eye

coma due to orbital tumors One of the tumors originated from the fronto ethmoidal sinus and two from the lacrimal gland one was a recurrent cystic adenoma another a cystic neurinoma localized in the apex of the orbit and the last was an undetermined orbital tumor Exophthalmos was found on the affected side in all cases mentioned The difference in tension between the normal and the affected eye ranged from 5 5 to 28 mmHg but glaucomatous defects of the visual fields were found in only two of these cases Congestion of the retinal veins was found in three cases and congestion of the episcleral veins in four cases

Nordmann et al (1961) described 14 cases of secondary glaucoma based on venous hypertension of extraocular origin Only one of these cases was due to an orbital tumor viz a meningeoma giving rise to a compression of the retro ocular veins

Case Report

Clinical notes

(O S H 100159) The patient is an 11 year old boy who at the age of 2 underwent an operation to remove a large congenital poorly demarcated cystic lymphangioma from the parotideo masseteric and mastoid regions The micro scopic examination showed numerous cystically dilated lumina of various sizes

angioma having been removed from the left parotideomasseteric and mastoid regions when the patient was about two years old and also the fact that the ipsilateral ptosis was observed already at that time indicate very firmly that the releasing factor is a branch of this tumor in the orbit even though the definite histologic proof is absent

No previous description has been given of monocular glaucoma based on retrobulbar lymphangioma However Birge (1968) reported a case in which a conjunctival lymphangioma affected the aqueous outflow at the chamber angle resulting in increased pressure

Ira Jones (1959) found 29 cases of orbital lymphangiomas in an analysis of 62 lymphangiomas of the ocular adnexa No increase of tension was noted in any of the cases This series besides reporting by far the greatest number of cases and rendering a complete historic review furthermore reveals that 10 of the 29 orbital lymphangiomas were present already at birth and the greater part of the remainder were diagnosed during childhood Only in 3 cases did the tumors manifest themselves in adulthood (at the ages of 27 38 and 44 respectively) All patients had exophthalmos Moreover the most prevailing symptoms were disturbances of the muscular balance and ptosis Jones stated that the lymphangiomas of the ocular adnexa constitute 20 % of all lymphangiomas and of the series of 62 presented by Jones the orbital group constituted 47 % (including some cases with concomitant extraorbital localization) It is remarkable that the series does not comprise elderly or middle aged patients still being controlled or treated for lymphangiomas which fact indicates that the progression ceases in early adulthood The lymphangiomas are benign radiorefractive tumors the treatment of which is therefore excision However surgery is difficult because the tumors are poorly demarcated and lack a well defined capsule An interesting feature of orbital lymphangiomas is the fact that lymphatics never have been demonstrated in the orbit and thus there is no explanation as to their origin In those cases which in addition to the orbital lymphangioma also have concomitant extraorbital tumors one might imagine that the orbital tumor were a branch of the extraorbital lymphangioma as also mentioned by Jones This however still does not explain the origin of the lymphangiomas localized in the orbit only

As far as the treatment is concerned there are two possibilities excision of the tumor or application of the usual ophthalmologic methods to control glaucoma such as miotics carboanhydrase inhibitors or a fistulating operation Surgical removal is made difficult by the poor demarcation of the tumors and their proximity to such delicate structures as the optic nerve and adjacent vessels and the nerves to the eye muscles In this connection it must be borne in mind that the lymphangiomas are benign tumors the progression of which

Eye examination

Vision in both eyes 1 00 emmetropy Left ptosis the upper eyelid covering ⅔ of the pupil The left globe protruded 3 mm but there was no other dislocation of the globe and eye movements were normal There was a slight retrobulbar resistance A slight anisocoria with a larger left pupil was observed but otherwise pupillary reactions were normal Tonometry by applanation showed the tension of the right eye to be 16 mmHg and of the left eye 38 mmHg A slight dilatation of the episcleral veins was found on the left side Gonioscopy showed open angles with normal structures An abundance of pectinate ligaments was seen on both sides of which many on the left side contained blood vessels. Ophthalmoscopy of the left eye showed a rather deep nonmarginal excavation intense pulsation of the central artery, and marked venous stasis The right fundus was normal No visual field defects were noted

Supplementary examination

X-ray examination of the skull and especially the orbits was normal A phlebography of the frontal vein showed a rather pronounced dislocation of the superior ophthalmic vein on the left side corresponding to a space occupying lesion temporally and posteriorly in the orbit The phlebography revealed no pathologic vessels or abnormal accumulations of contrast Left carotid arteriography left contrastorbitography and pneumoorbitography revealed no abnormalities

No treatment was started and at the following half yearly checkups the condition was found to be more or less unchanged until January 1971 at which time incipient glaucomatous visual field defect of the lower nasal quadrant could be demonstrated An attempt was then made to obtain a biopsy through an anterior orbitotomy but it was not possible to gain access to the hindmost part of the orbit After having discussed the case with the neurosurgical department it was decided not to perform a Kroenlein operation or a transfrontal intervention due to the risk of damaging sight or motility Instead of surgery treatment was started with pilocarpine drops 2 % 4 times daily by which procedure a decrease of the tension was obtained to a level of about 20 mmHg

Discussion

The unmistakable signs of venous stasis of the left eye in the described case hardly leave any doubt that the left glaucoma was caused by extraocular venous obstruction localized in the orbit as both the exopthalmos and the dislocation suggest the presence of a growth in the orbit A large cystic lymph

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CONGENITAL IRIS CYST

A Case Studied by Light and Electron Microscopy

BY

J HVIDBERG HANSEN and F ERLIN LARSEN

A case of unilateral iris cyst in an infant aged three months is reported The cyst was excised and subjected to light and electron microscopy the results of which verified the analogy of the cystic wall with the conjunctival epithelium which likewise was examined Further proliferations of pigment epithelium were found along the pupillary border Most likely some of the iris cysts are due to aberrant conjunctival epithelium which possibly had invaded the chamber in connection with the formation of the lens vesicle

Key words congenital iris cyst – electron microscopy – goblet cells – conjunctiva

Congenital iris cysts which may be pigmented or non pigmented manifest themselves clinically within the first few months of life or later in infancy Differentiating them from traumatic and idiopathic (*spontaneous*) cysts is not easy and becomes increasingly difficult with increasing age of the *child*

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ceases at puberty (Ira Jones) and that the pressure in many cases can be controlled by the usual medical or surgical treatment of glaucoma (Bietti & Vanni)

In the case reported here it is remarkable that such a marked decrease in pressure was obtained by using pilocarpine only The cause of the glaucoma in this case lies peripherally to Schlemm s canal and the trabecular meshwork must be considered normal It is well known that pilocarpine lowers the pressure both in glaucomatous as well as in normal eyes although this effect is less pronounced in the normal eye Pilocarpine may possibly affect the vessels as well as the trabecular meshwork a fact which has been mentioned in various previous reports but which has not yet been proved sufficiently

Bietti & Vanni suggest that the correlation between orbital tumors and secondary glaucoma is far more frequent than is generally assumed due to the fact that it is very often not recognized Since the establishment of a separate department dealing with exophthalmos and orbitotonometry at the ophthalmologic clinic in Rome they have with certainty found differences in pressure of the two eyes and sometimes onsetting functional failure

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Fig 1

Left eye with iris stroma cyst Fig 1a shows the size when the patient was 3 1/2 months old and Fig 1b the size at the age of 7 months Finally Fig 1c illustrates the condition after mydriasis Minor dark projections are just discernible behind the pupillary border along the upper boundary of the cyst

Mydriasis revealed pigmented cyst like formations along the nasal pupillary border (Fig 1c) Tension in general anaesthesia (fluothane N O O) pre operatively 91 mmHg o u (Schiotz) By means of a limbus based conjunctival flap the chamber was opened without perforating the cyst and radial incision was made of the iris at 6 30 and 10 30 The cyst adhered inferiorly to the cornea where a thin bridge of tissue had to be cut Peripherally the iris was cut and pulled free from its root During this process the cyst burst and its watery contents escaped At the conclusion of the operation a little blood was seen in the chamber and on the second postoperative day the chamber was full of clots which became totally absorbed in the course of nine days On the day of the patient s discharge slit lamp exam nation revealed a membraneous formation from 9 to 12 o clock having contact with the posterior corneal surface and from 12 o clock towards the centre a similar shaped structure Ophthalmoscopy showed red reflex but no details On subsequent control the stated membranes were found to have spread in the chamber On the latest examination of the patient five months after the operation the temporal half of the cornea and lens were clear A biopsy specimen was taken from the conjunctiva in the inferior fornix of the left eye

Method

The removed cystic tissue together with the excised part of the iris immediately after the removal were placed in 5 % glutaric aldehyde adjusted to pH 7 3 with cacodylate buffer The tissue was primarily fixed in this for 24 hours Subsequently fixation was performed with osmium tetroxide and the tissue was embedded in araldite after the usual dehydration Sections were stained with zincuranylacetate 1 % and leadcitrate 1 % (Venable & Coggeshall 1965) For light microscopic examinations we used 1 to 2 microns thick standard sections cut on a LKB microtome and stained with toluidine blue Electron microscopic studies were made in a JEM T electron microscope

Stromal cysts manifest themselves as vesicular formations on the anterior surface of the iris projecting into the anterior chamber where they may reach the posterior corneal surface The cysts may remain stationary or often may grow in size and then cause secondary glaucoma The differential diagnosis from malignant tumours and specific nodular inflammations ought to be considered Disagreement prevails with regard to the aetiology of congenital iris cysts Ectoderm neuro ectoderm and mesoderm have all been suggested as histogenetic possibilities

The disease must be regarded as rare In the Scandinavian literature we have found no descriptions of congenital iris stroma cysts in young infants but Jensen reported a case from Denmark at the meeting of the European Ophthalmic Pathology Society in 1969

Case Report

The patient a boy was the second of two children born one week after the expected term There are several cases of cataract among the mother s relatives though none congenital The mother herself has harelip Apart from external version the pregnancy was uncomplicated The parturition was started with rupture of the membrane of a distended membranous sac having an orifice of 2 cm Pudenal nerve block was performed but not paracervical anaesthesia Birth weight 2850 g

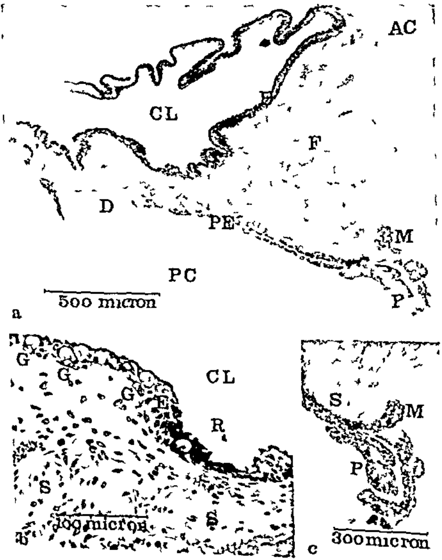
The patient developed normally He had frequent catarrhal periods and at the age of two and a half months he developed a purulent conjunctivitis most pronounced in the left eye and effectively treated with chloramphenicol

When the patient was three months old his mother noticed a spot on the nasal part of the left iris On his admission 14 days later this spot had allegedly grown in size Physical examination then showed mild conjunctival congestion in both eyes parallel axes and normal sized eyes The right eye was normal The left eye had a normal cornea On the upper nasal quadrant of the iris a cystic non pigmented ovoid growth was seen measuring 6 by 5 mm and reaching almost as far as the pupillary border which was flattened Peripherally the cyst extended to the angle (Fig 1 a) Through the pellucid cyst the iris stroma was seen to be finely vascularized towards the pupil Anteriorly the cyst was in contact with the posterior corneal surface Tension (Schiotz) in both eyes was 17 mmHg Diascleral transillumination showed only very slight pellucidity of the iris at the site of the cyst Ophthalmoscopy in mydriasis normal conditions

On admission for control one month later (4 ½ months old) the cyst had grown a little (6 5 by 5 mm) It had spread towards the pupillary border and the cyst wall presented fine vessels

At the age of seven months the patient was admitted for operation The cyst had now grown to 9 5 by 5 5 mm and the pupil had become displaced down and temporally (Fig 1 b)

found to be empty The pigment epithelium on the posterior surface of the iris had an appearance normal to the age of the patient with relatively sparse pigmentation No pigment containing cells were seen in the iris stroma Towards the periphery of the iris transition was seen to an epithelium with light cells against the posterior chamber and under this was observed a pigmented cell layer pre enting a few typical ciliary processes situated at the extreme



The conjunctival biopsy specimen from the inferior fornix of the same patient was examined in a similar manner To secure a known orientation during the cutting a special embedding technique was employed (Hvidberg Hansen 1970)

Results

1 Light Microskopy

The iris was cut partly radially at the site of the cyst and partly as a chord in the iris along the nasal and temporal borders of the cyst to permit observation of the transitional zones to normal iris tissue The walls of the collapsed cyst consisted of an epithelium of 2–4 layers with cuboid to low columnar cells basally and more flattened cells towards the lumen of the cyst The surface was slightly folded in this place The cyst was surrounded by a connective tissue containing numerous distended vessels

A section from the close pupil border of the cyst displayed a triangular tissue area (Fig 2 a) corresponding to a thickening of the connective tissue surrounding the cyst This was verified in serial sections Neither nervous nor muscular tissue was observed close to the cyst but transition to a normal iris stroma was seen at the posterior side of the cyst In this region i e off the site where the cyst adhered to the iris the epithelium was observed to contain several typical goblet cells (Fig 2 b) which proved to be PAS positive In the remaining part of the cyst goblet cells were more sporadically present Such were even practically absent within large parts of the anterior wall In various places the basal epithelial cell layer of the cyst wall was stained more dark and displayed a somewhat looser structure of the cytoplasm as compared with the upper cell layer towards the lumen The cyst lumen was

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Fig 2

Light microscopic survey of the iris with cyst tissue Fig 2 a shows the lumen of the cyst (CL) enclosed by 2 or 3 layers of epithelium (E) provided with a very thin layer of connective tissue along the side turning towards the anterior chamber (AC) A larger mass of connective tissue (F) is seen at the pupillary margin (M) The pigmented epithelium (PE) of the iris is defective at (D) (artefact) Proliferated pigment epithelium (P) projects into the posterior chamber (PC) Fig 2 b represents a higher magnification which shows goblet cells (G) in the epithelium (E) off the sphincter iridis (S) The lumen of the cyst (CL) is empty except for an erythrocyte (R) Fig 2 c illustrates the pigment proliferations (P) along the pupillary margin (M) at the close pupil boundary of the sphincter fibres (S) The nuclei appear light owing to the considerable amount of pigment contained in the cytoplasm

bouring cells and of cells from the upper and the basal layers Numerous desmosomes as well as occlusion and adhesion zonules were seen between the cells especially apically Towards the lumen a brush border was found with 0 5–1 micron long microvilli covered by a fibrillar material (Fig 6)



periphery of the preparation Proliferations of pigment epithelium with no cyst formation were found along the pupillary border (Fig 2 c) The pigmentation was slightly more intense here than in the remaining pigmented epithelium Here and there the pigment cells were arranged in papillomatous formations having two layers of cells without connective tissue base Light microscopy of the *conjunctival biopsy* specimen revealed an epithelium consisting of 4 to 6 layers of which the surface layer contained numerous goblet cells The individual epithelial cells were rather uniform and loose connective tissue was seen under the epithelial layer

2 Electron Microscopy

Different parts of the cyst were examined and found to have in principle the same structure The number of cell layers in the epithelium varied however with most specimens having two or three layers and variations were also noticed with regard to occurrence of goblet cells corresponding to the findings made in light microscopy

The basal part of the epithelium consisted of a layer of morphologically uniform cells the electron density of their cytoplasm being relatively homogeneous and fairly dense (Fig 3) There was no evidence to suggest presence of two or more morphologically different cell types Their nuclei were indented and centrally situated The usual cytoplasmic components were found including a moderately developed Golgi zone Among the cell content there is also reason to mention tonofibrils which were present in large numbers in certain parts of the cyst located just above the basal membrane The cells were generally well defined with relatively smooth cell boundaries Interdigitations did occur however between the cells especially in the upper parts of the cells In the luminal cell layer two cell types were found of which one had the appearance of typical goblet cells The remaining cells could not be divided into subgroups despite differences in cytoplasmic density because there was no fundamental nor any essential quantitative difference in their content of organelles The luminal cells were in the main less electron dense than the basal but the nuclei were of the same configuration as in the basal cell layer The cell boundaries were characterized by *interdigitations of neigh*

Fig 3

Electron microscopic survey of the cyst epithelium A filled goblet cell (G) with nucleus (Q) projects into the cyst lumen (CL) which is empty Two layers of epithelial cells are seen The nuclei in the basal layer are marked (B) and those in the luminal (L) The luminal cell layer is provided with numerous microvilli Arrows point towards interdigitations of the epithelial cells



Fig

Electr n microscopic survey of conjunctival epithelium Several goblet cells (G) are seen Towards the lumen of the fornix (FL) m crovilli are seen and in the cytoplasm ves el s (arrow) Sim lar vesicles are also pres nt n some of the epithelial cells m re b sally e p off the asteri k Nuclei n epithelial cells are marked N and in goblet cells Q

Electr n micr scopy of the conjunctival epithelium revealed principally the same m rphol gical features as described for the epithelium of the cyst wall (Fig) No detailed description will be given of the fine structure of the c njunctival epithelium but there is reason to point out that the basal

Most of the luminal cells had in their apical cytoplasm characteristic vesicles 0 2–0 4 micron in size with an eccentrically located very electron dense "nucleus" and otherwise granular content (Figs 4 6 a) Several cells presented transitional forms between such vesicles and others more superficially located with more finely granular contents and without the eccentric condensation Further invaginations of the surface membrane containing a structure identical to that covering the microvilli were seen

In the cells a fairly well developed Golgi apparatus was found apical to the nucleus (Fig 4) Vesicles of the appearance of lysosomes were noticed in several cells The cells of the layer generally had a prismatic shape and no nerve cell elements nor melanoblasts were observed in the epithelium neither basally nor luminally The lamina propria consisted of loose connective tissue varying in thickness with vessels and fibrocytes of normal appearance

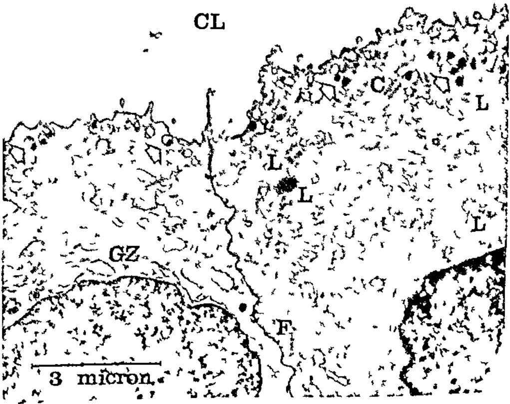


Fig 4

Detail of luminal epithelial cells Arrows mark several vesicles with electron dense contents close to the cell membrane turning towards the cyst lumen (CL) Further a Golgi zone (GZ) lysosome like formations (L) and tonofibrils (F) are seen Finally a centriole (C) is visible

18 cases The majority of the histological analyses showed the wall of cysts located at the stroma to consist of stratified cuboid to columnar epithelium surrounded by connective tissue Some writers claim to have noticed goblet cells (Koch 1971 Bayadi & El Defrawi 1965 Nauman & Green 1967 Jensen 1969) Nauman & Green described another case in which no goblet cells were detectable in the cyst Neither were such cells found in a cyst described by Roy & Hanna (1971) nor in one described by Kolman (1969) Cysts have been described with a microscopical picture corresponding to that of epidermoid growths and with greasy contents (Paufique Bonnet & Montibert 1964 Reese 1963) Recently the results were reported of electron microscopy of a congenital iris cyst (Roy & Hanna 1971)

The aetiology of stromal cysts observed in the iris of infants has been a subject for discussion The problems concentrate on two principal questions are the cysts of traumatic origin or are they due to a proper developmental abnormality and if the latter are they of ectodermal or neuro ectodermal derivation?

It is often difficult to preclude the possibility that previously disregarded perforating injuries may have caused implantation of epithelial elements with subsequent cyst formation in the anterior chamber particularly in the cases of cysts noticed in fairly old children or adults

Maumenee & Shannon (1956) doubt that perforating injuries have been effectively precluded in previous studies of iris cysts In our case where the cyst was detected when the infant was three months old no information was available on previous injury Neither did physical examination disclose any signs of sequelae of such A perforating injury must therefore be regarded as unlikely in the case under review

During the development of the eye its anterior part is exposed to invaginations from surface ectoderm and neuro ectoderm respectively There is a theoretical possibility of faulty ablation of cells from both structures (Politzer 19 3 Mann 1957) A hypothesis of mesodermal origin has receded within recent years (Mann 1957) Duke Elder (1964) stated that stromal cysts generally are believed to originate from the surface epithelium but that a more intimate relation to the lens formation is a possibility and finally that the cysts may originate from the border of the optic cup The cysts attached to the pars iridica retinae might be caused by the failure of the two layers in the primary optic vessels to close The so called marginal sinus (v Szily) has thus been considered as the starting point of cyst formation (Mann 1957) Be it mentioned however in this connection that recent studies of well fixed specimens have been unable to prove the existence of this cavity (Hvidberg Hansen 1971)

The epithelial structure of the cyst wall does not as such afford a basis



Fig 6

Detail of the luminal aspects of cyst epithelium (a) and conjunctival epithelium (b and c) Fig 6 a shows in addition to some vesicles with condensed contents a lysosome like body (L) In Fig 6 b as in 6 a signs of phagocytosis are seen at the arrow connection to the fibrillar matter on the microvilli being present and visible most plainly in Fig 6 c Magnification was the same for all three pictures

layers were found to contain tonofibrils Such also occurred in the other layers but in smaller numbers Further mention should be made of the fact that in the apical cell layer we observed numerous microvilli measuring 0 5-1 micron in length and 0 1 micron in diameter In the apical cytoplasm vesicles with granular contents were seen and not infrequently with a condensed nucleus like eccentrically located formation (Fig 6 c) Such vesicles were also occasionally seen in cells located in the middle layer or at a deeper level in the luminal cells (Fig 5) Typical goblet cells were found in the uppermost epithelial layer

Discussion

The first descriptions of congenital iris cysts were published about the middle of the nineteenth century A historical review is found in comprehensive symposia by Tertsch (1914) and Villard & Dejean (1933) The former reported 51 cases the first of which was from 1833 and the latter reported another

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for a distinction between ectodermal and neuro ectodermal derivation In Roy & Hanna s (1971) opinion the ultrastructure of the epithelial cells suggests a neural derivation In our case was found an epithelium which both light microscopy and electron microscopy showed to be identical with conjunctival epithelium as assessed by comparison with that described in the literature (Wanko et al 1964 Radnot 1971) and the result of our examination of a conjunctival biopsy specimen from the same patient Note however that neither melanoblasts nor nervous tissue were observed in the epithelium of the cyst

For the moment the finding of goblet cells seems to be a decisive factor in the pathogenesis These cells argue against a histogenetic association with neuro ectoderm and also seem to render any close relations to the lenticular epithelium unlikely It should be emphasized that in large sections of the cyst goblet cells were scarce and further, they were localized in clusters in the part of the cyst turning towards the iris stroma Similarly in a case described by Jensen (1969) only few goblet cells were found in serial sections examined This demonstrates how careful one should be with the histological examination of iris cysts

Comparison of our case with pictures and description of the ultrastructure of the cells in Roy & Hanna s (1971) paper dealing with a congenital iris cyst showed several points of resemblance between the two Most important was the occurrence of numerous microvilli of an appearance corresponding to that observed by us both in conjunctival epithelium and in our cyst Further the apical cells displayed in their luminal parts minor cysts highly reminiscent of the cysts we found both in the conjunctival and in the iris cyst epithelium Roy & Hanna also described intracellularly located filaments of the appearance of tonofibrils analogous to the findings in our preparation and likewise described in detail by Wanko Lloyd & Mathews (1964) Fibrils of this appearance occurring in such numbers are not a common phenomenon in ocular neuro ectodermally derived tissue e g the iris pigment epithelium To summarize the epithelium in the case described by Roy & Hanna also seems likely to have been of conjunctival origin It may be surprising that the cyst found by us contained nothing relating to secretion from goblet cells The material covering microvilli might be conceived to represent goblet cell secretion Furthermore the cystlike formations in the luminal parts of the epithelial cells possibly indicate phagocytosis of the cystic contents adhering to the surface membrane The lysosome content might bear out this theory

The pigment proliferations along the pupillary border are of the same structure as seen in children under treatment with miotics especially those treated with irreversible cholinesterase inhibitors (Christensen Swan & Huggins 1956)

Our patients was treated with no such drug and we have no explanation of the phenomenon

The final clinical course has not yet been clarified The whitish membranes observed in the chamber after the operation may be due to incomplete removal of the cystic wall The orifice of the cyst was visible histologically (Fig 2) Implantation of liberated cells *from* the cyst is a possibility that has been considered but this process is not very likely

Iris cysts become increasingly difficult to remove the more they have grown in size Duke Elder (1966) states that one can expect excision to be successful only if the cyst is small and localized in the close pupil section leaving a zone with normal iris tissue at the root Cases have been described however in which the cyst has not recurred even after incomplete resection

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ENDOGENOUS MYCOTIC RETINOPATHY

Report of a Case

BY

A HVIDBERG HANSEN

A case with metastatic spread of *Candida tropicalis* infection to the eyes of a patient with ulcerative colitis is presented The ocular changes are dominated by white snowball like foci in the retina and vitreous and by prepapillary and preretinal connective tissue bands Fluorescein angio graphy was performed The patient was treated with Amphoterecin B and 5 Fluorocytosine The ophthalmoscopic changes were stationary 9 months after this treatment

Key words mycot c retinopathy – endogenous mycotic eye infection – intraocular fungus infection – antimycotic treatment

Mycotic infections may reach the interior of the eye by three routes 1 Infec tion from the outside e g from a fungal conjunctivitis or fungal keratitis 2 Direct infection by perforating wounds either accidentally or surgically 3 Endogenous infection where the fungi are spread to the eye by the blood stream

The first two routes of infection are not common but the endogenous mycotic endophthalmitis is even more rare Actinomycete blastomycete and aspergillus are the causative organisms most frequently but fungi of the candida types have been reported to produce endogenous eye infections as well (Wolter 1962 Tarkkanen et al 1967 Wälinder & Kock 1971)

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Fig 1



Fi

The purpose of this communication is to describe an illustrative case of endogenous mycotic retinopathy caused by *Candida tropicalis*

CASE REPORT

The patient was a 37 year old woman who had been treated for an ulcerative colitis since 1962 In October 1970 she was admitted to a surgical department (j nr 21 06 33-0126) with severe symptoms of ulcerative colitis which was treated with prednisolon clysmata for 2 weeks Coleproctectomia was performed and large doses of antibiotic (neomycin penicillin and streptomycin) were given pre and postoperatively

The general condition was bad and 6 weeks after the operation the patient was febrile with spiking temperature Blood cultures were performed several times There were no growths of bacteria but in all cultures yeastlike fungi were found The fungi were identified as *Candida tropicalis* Treatment with Amphotercecin B (total 350 mg) was started The general condition improved gradually and the patient was discharged three months after the operation

Eye signs

During the septic condition after the operation the patient noticed diminishing vision in the right eye but she did not complain of this until one month later Eye examination in January 1971 showed

Visus o d Hand movements in front of the eye
Visus o s 0 4 + 1 00 sf

Anterior segments No signs of inflammation

Ophthalmoscopy o d The anterior part of the vitreous body was clear The disc was covered by vascularized connective tissue bands from where naked new vessels stretched somewhat into the vitreous body In the macular region were one big (one p D in diametre) and two smaller white snowball like lesions with indistinct filamentous borders The prepapillary connective tissue bands stretched towards these foci

Ophthalmoscopy o s Very slight connective tissue veil in front of the papilla Between the disc and the macula were two white foci and over the macula was seen a third focus all were of the same type as on the right side but smaller (Fig 1)

Amphotercecin B treatment was started again for 6 weeks (total 750 mg) During this treatment the white foci diminished and the borders became less indistinct but the prepapillary connective tissue bands gradually increased and in the right eye reached and covered the white foci in the macular region (Fig 2) Prednisolon 30 mg/day was given in an attempt to limit the connective tissue proliferation into the vitreous This treatment was discontinued after 10 days as an aggravation of the fungal eye infection was feared Gradually the white foci protruded more into the vitreous body and from the top of each naked vessels stretched forward Amphotercecin B was given for a third period but after two weeks the treatment (total 210 mg) had to be discontinued as the serum creatinine level was increasing (1 0–2 9 mg/100 ml)

In the right eye there was a large vasculated connective tissue proliferation which

A new oral antimycotic substance is 5 Fluorocytosine It has shown effective antimycotic activity in several cases of generalized candidiasis Richards et al (1970) have described a case of corneal and intraocular infection of *Candida albicans* where 5 Fluorocytosine treatment was effective In the present case 5 Fluorocytosine treatment was started late in the course of the disease Because of the location of the lesions it was not possible to determine whether the progress in the ocular changes before the treatment was due to active fungal infection or due to scar formation The ophthalmoscopic changes and the visual acuity have however remained stationary since this last treatment

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protruded into the vitreous and covered both the disc and the macular region. In the left eye each of the white foci protruded into the vitreous and lay in front of a conical connective tissue band. Between the foci these bands formed a tentlike figure as if a string between the foci was drawing the posterior face of detached vitreous somewhat forward. The prepapillary connective tissue did not increase in the left eye.

Fluorescein angiography of the left eye was performed in June 1971. Fluorescence at the borders of the white foci started in the beginning of the venous phase. Little-by-little the foci became fluorescent in the centre as well, and from small vessels between the foci fluorescein was leaking.

In June treatment with 5-Fluorocytosine was started (125 mg/kg per day, total 125 g). There were no side effects of this treatment. The ocular changes were stationary and the visual acuity was observation of hand movements in the right eye and 0.9 in the left eye. A later control 9 months after this last treatment has shown no signs of progression.

Discussion

The ocular changes in endogenous endophthalmitis are characteristic and one may postulate the etiology from the ophthalmoscopic changes. In the present case the changes correspond with the findings described in other publications except for the prepapillary and preretinal connective tissue bands which are so dominating in this case. These bands are much like the connective tissue bands which are seen in cases of proliferative diabetic retinopathy. The patient does not have diabetes mellitus.

Histopathological examinations of similar lesions (Van Buren 1959, Mc Lean 1963) have shown that the white snowball-like affections are mycotic abscesses localised on the retina and the vitreous body. In the centre the abscesses contain inflammatory cells (both polymorphonuclear and mononuclear), necrotic tissue and yeast elements in both hyphal and budding forms.

The prognosis for mycotic endogenous endophthalmitis is bad and in many cases enucleation is performed. The two most effective fungistatic drugs which may be useful in treatment of ocular fungus infections are Amphotericin B and Nystatin (Rheins et al. 1966). Neither drug penetrates the normal eye satisfactorily by any route. Both substances are highly toxic and direct intraocular injection gives an intense reaction with risk of subsequent permanent damage to the eye (Wålinder & Kock 1971). Cases with healing of the fungal abscesses *after treatment* with Amphotericin B have been described (Bonatti et al. 1963, Viallefont et al. 1968, Wålinder & Kock 1971). In all these cases there were scar formations in the eyeground and as the abscesses apparently have a tendency to localize near the macular region, vision was considerably reduced.

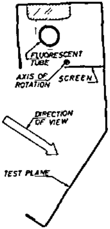


Fig 1
Cross section of illumination box.

box equally suitable for clinical and laboratory use When used in a dark room, the light box meets the above recommendations and at the same time it ensures optimal and comfortable testing conditions

Methods and Results

Design

Because of the oblong configuration of most colour vision tests a fluorescent tube i a more practical light source than an array of incandescent lamps combined with filters The fluorescent tube used here is a standard commercial tube of 590 mm length with a colour temperature of 6500 K and a colour rendering index $R_a = 93$ (cf Bouma 1971) accord ng to the manufacturer s specifications This light source is in these contexts an adequate approximation of the CIE Standard Illuminant D

The tube and its standard fixture are mounted in the upper part of a box like alu min um enclosure in such a way that the tube is screened from direct view (Fig 1) A switch s nterposed in the mains supply The lower part of the box forms an incl ned plane supporting the test material (Farnsworth s assorting tests require the add tion of a simple support, Fig 2) A sc een is fastened inside the box, below and beh nd the fluorescent tube in order to equalize the illu mination over the inclined plane The angle of light incidence is approximately 45 degrees as recommended by the CIE

The illum nation box is mounted on a s mple floor stand in such a way that it can be turned around a horizontal axis just below the fluorescent tube (Figs 1 and 2) A locking device allows the setting of attitude at will The attitude is individually adjusted so that the inclined test plane becomes perpend cular to the line of sigh

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ILLUMINATION BOX FOR COLOUR VISION TESTS

BY

L. FRISÉN and A. HEDIN

An arrangement for the appropriate illumination of colour vision tests is described. It is intended for clinical and laboratory use.

Key words: colour vision – vision tests – instrumentation – illumination

The time honoured use of natural daylight for the illumination of pigment based colour vision tests has several obvious disadvantages. Natural daylight varies not only in availability but also in intensity and colour temperature. These variations are capable of considerably influencing the outcome of the tests (Schmidt 1952). The use of artificial standardized light sources is therefore preferable (Schmidt 1952, Priklonsky 1961, Frey 1964).

Standardized illuminants similar to northern daylight have been defined by the Commission Internationale de l'Eclairage, CIE (Standard Illuminants C and D). Comparable artificial light sources are now universally available and are also allowed or recommended by the great majority of manufacturers of colour vision tests.

Recommendations as to the intensity of illumination range over 100 lx to 1000 lx with values around 300 lx being most frequent (Frey 1964). Appropriate geometric conditions of illumination and viewing have been defined by the CIE.

The recommendations listed above are rather awkward to meet with available equipment. This has prompted the development of a simple illumination

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Measurements

Illumination and luminance characteristics were measured with the aid of a Metrux K Illumination Meter (Metrawatt A G Nurnberg) The measurements were made in a dark room The results of the illumination measurements are given in Fig 3

The illumination levels corresponded to luminance *levels of 45 to 90 cd/m² in the* center of various pseudo isochromatic charts

Discussion

Fluorescent tubes with colour temperatures and colour reproduction characteristics similar to CIE s Standard Illuminants C or D are more practical than combinations of incandescent lamps and filters in the illumination of pigment based colour vision tests Their low cost low working temperature and high mechanical resistance are favourable factors and their dimensions ensure an even illumination also of tests with an oblong configuration e g Farnsworth s assorting tests The light output does not deteriorate for at least 1000 hours of use A change of tube every year should therefore guarantee a virtually constant illumination under usual working conditions

Table I

Recommended light sources and levels of illumination for various colour vision tests as stated in the manufacturers manuals

Name of test	Recommended light sources	Recommended levels of illumination
Farnsworth s		
D 15	6500 K or north daylight	–
100 Hue	6500 °K or north daylight	≧ 270 lx
Tritan Plate	average daylight or equivalent	–
Bostrom Kugelberg	daylight or equivalent	–
Dvorine	daylight or equivalent	–
Hardy Rand Rittler	6700 K or equivalent	100–650 lx
Rabkin	artificial daylight	–
Tokyo Medical College	daylight or daylight fluorescent lamp	≧ 100 lx
Velhagen	daylight	–

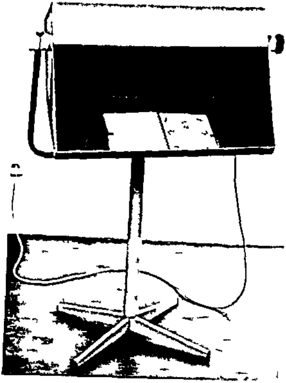


Fig 2
The illumination box front view

of the subject to be tested as recommended by the CIE This arrangement is more practical than a height adjustment The height above the floor is appropriate for seated subjects The floor stand is offset to admit the subject s knees (even if seated in a wheel chair) below the illumination box

The interior of the box was painted with a matt neutral grey paint with a reflection factor of 25 per cent throughout the visible spectrum

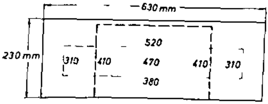


Fig 3
Test plane illumination in lux The heavy broken lines correspond to a spread of average pseudo isochromatic charts the fine broken lines to the outlines of one Farnsworth Munsell 100 Hue sample box

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Illumination and luminance characteristics were measured with the aid of a Metrux K Illumination Meter (Metrawatt A G Nurnberg) The measurements were made in a dark room The results of the illumination measurements are given in Fig 3

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Rabkin	artificial daylight	–
Tokyo Medical College	daylight or daylight fluorescent lamp	≧ 100 lx
Velhagen	daylight	–

The validity of high colour temperature fluorescent tubes as illuminants for colour vision tests has been amply documented (Sloan 1945, Schmidt 1952, Frey 1964). A majority of test manufacturers also allow or recommend artificial light sources with these characteristics (Table I).

The advantages of fluorescent tubes are best exploited in suitable designed illumination boxes. Such a box should screen the tube from direct view and it should meet the recommendations of CIE with respect to angles of light incidence and viewing. It should also supply a neutral background with a *suitable and uniform luminance level. The box described here fulfills these* requirements. Although such a box excludes much environmental light it should be used in an otherwise unlit room to ensure optimal and constant testing conditions. This cannot be achieved with natural daylight. The use of the latter light source will unnecessarily introduce several unwanted variables capable of impairing the reproducibility of pigment based colour vision tests.

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NAUSEA AND VOMITING AFTER OCULAR SURGERY

BY

P NIKKI and S POHJOLA

The frequency of postoperative nausea and vomiting following common ocular operations was studied in 110 male and 12 female patients anaesthetized by four d fferent techniques N_2O-O_2-relaxant anaesthesia neurolept analgesia N O-O₂-halothane anaesthesia and local anaesthesia with ? ‰ mepivacaine There were no significant differences between these various techniques in regard to the frequency of nausea and vomiting although local anaesthesia seemed to give the best results in this respect

In the second part of the study the antiemetic effect of dehydrobenzperidol was studied in 127 male and 175 female patients A dose of ?.5 mg of this drug was effective in preventing postoperative vomiting both after N O-O relaxant anaesthesia and more distinctly after local anaesthesia

Key words nausea – vomiting – ocular surgery – dehydrobenzperidol

Vomiting is a dangerous complication in intraocular surgery because by increasing the intraocular tension it may give rise to prolapse of the iris wound rupture and even intraocular bleeding Furthermore it has been reported by Borchert & Dauss (1971) to occur more often after ocular than any other type of surgery Therefore we wanted to compare various anaesthetic techniques in regard to postoperative sickness and to elucidate whether dehydrobenzperidol

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is effective as an antiemetic also after surgery performed under local anaesthesia as it was after N_2O–O_2 relaxant anaesthesia (Nikki & Pohjola in press)

Material and Methods

The first part of the study was performed on 235 patients and the second part on 302 patients In the first part 110 male and 125 female patients were anaesthetized for common ocular operations (mainly those for cataract retinal detachment squint and glaucoma) using four standardized anaesthetic techniques as follows

I N O–O d tubocurarine
II Neurolept analgesia
III N O–O halothane
IV Local anaesthesia

Details of the anaesthetic techniques

I Premedication with pethidine 1 mg/kg and atropine 0 01 mg/kg Induction with thiopental sodium 5 mg/kg intubation with suxamethonium 1 mg/kg maintenance of anaesthesia with N_2O–O_2 mixture (75 and 25 %) intermittent positive pressure ventilation (IPPV) using either d tubocurarine (0 3–0 5 mg/kg) or pancuronium (0 05–0 1 mg/kg) as relaxant and at the completion of anaesthesia 1 mg of atropine and 2 mg of neostigmine for the reversal of relaxation

II Premedication with dehydrobenzperidol in a dose of 2 5–3 75 mg and fentanyl 0 05–0 075 mg Induction with 10–15 mg of DHBP and 0 20–0 30 mg of fentanyl Maintenance of anaesthesia and its completion as in technique I

III Premedication and induction as in technique I Maintenance with N O–O_2 mixture with 1–1 5 % of halothane Spontaneous or assisted ventilation

IV Premedication as in techniques I and III Akinesia and retrobulbar anaesthesia with 120–200 mg (6–10 cc of 2 %) mepivacaine

In the second part of the study the effect of 2 5 mg of dehydrobenzperidol (Orion Oy Helsinki) on postoperative nausea and vomiting was tested by administering it intramuscularly 10–15 min before the completion of operation under anaesthesia by techniques I and IV This part of the study was performed on 127 male and 175 female patients The age distribution of the different male and female groups to be compared was similar in both the first and the second part of the study

Nausea score

The nausea and vomiting of each patient was evaluated by ward nurses during consecutive periods of 3 hours in the course of a 12 hour period with application of the following scores

0 point = no nausea
1 point = nausea no vomiting
2 points = retching one or two attacks of vomiting
3 points = repeated attacks of vomiting

Thus the maximum score was 12 indicating that the patient was subjected to frequent attacks of vomiting throughout the entire 12 hour period

Statistical treatment

The results of men and women were tested separately with χ^2 for fourhold table and with Yates correction for continuity

When the lowest expected frequency was less than five the hypergeometric distribution (Fisher exact test) was used The separate fourhold tables for males and females were tested together by the procedure presented by Mantel & Haeszel (1959)

Results

Part I

The frequency of nausea and vomiting was higher in females than in males regardless of the anaesthetic technique used (40–55 % in females and 15–30 % in males)

Table I
Postoperative nausea in female patients after ocular surgery using different anaesthetic techniques

Method	Number of patients	Vomiting (patients)	Nausea (patients)
$N_2O + O_2$ + rel	29	14	3
Neurolept analgesia	29	11	5
$N_2O + O_2$ + rel	33	12	3
$N_2O + O_2$ + halothane	34	8	6
$N_2O + O_2$ + rel	31	12	4
Local anaesthesia	29	5	7

is effective as an antiemetic also after surgery performed under local anaesthesia as it was after N_2O-O_2 relaxant anaesthesia (Nikki & Pohjola in press)

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Table IV

Effect of dehydrobenzperidol on postoperative nausea after ocular surgery in local anaesthesia

Method	Number of patients	Vomiting (patients)	Nausea (patients)
Male			
Local anaesthesia	21	2	3
Local + dehydrobenzperidol	24	1	1
Female			
Local anaesthesia	43	15	4
Local + dehydrobenzperidol	43	4*	1

$p < 0.01$

Part II

As seen in Table III dehydrobenzperidol in a dose of 2.5 mg intramuscularly reduced significantly the frequency of nausea and vomiting after N O–O relaxant anaesthesia during simultaneous statistical testing of both sexes ($p < 0.05$) Eight of 47 female patients had vomiting after DHBP whereas 19 of 47 female patients in the control group vomited In males the difference was less distinct

Most effectively DHBP acted after local anaesthesia four of 43 female patients had vomiting after DHBP whereas 15 or 43 in the control group females vomited The difference was significant ($p < 0.01$) In the simultaneous statistical testing of male and female *patients the difference was even more* distinct ($p < 0.001$)

When the four 3 hour periods were tested separately most attacks of nausea and vomiting were found to occur from 3 to 6 hours after all the anaesthetic techniques after which the frequency of vomiting and nausea diminished gradually

Discussion

A rather high frequency of postoperative vomiting and nausea was observable in the present series as well as in the paper of Borchert & Dauss (1971) who in more than 50% of patients aged from 1 to 14 years observed vomiting and

Table II
Postoperative nausea in male patients after ocular surgery using different anaesthetic techniques

Method	Number of patients	Vomiting (patients)	Nausea (patients)
$N_2O + O_2$ + rel	23	6	1
Neurolept analgesia	21	5	1
$N_2O + O_2$ + rel	30	8	3
$N_2O + O_2$ + halothane	34	9	3
$N_2O + O_2$ + rel	30	7	3
Local anaesthesia	25	–	3

The various anaesthetic techniques did not reveal significant differences in either female or male patients with the exception that both sexes seemed to have less vomiting after local anaesthesia than after N_2O–O_2 relaxant anaesthesia. The combined score of nausea + vomiting did not differ significantly in these two anaesthetic techniques.

Table III
Effect of dehydrobenzperidol on postoperative nausea after ocular surgery in $N_2O + O_2$ + rel anaesthesia

Method	Number of patients	Vomiting (patients)	Nausea (patients)
Male			
$N_2O + O_2$ + rel	39	8	4
$N_2O + O_2$ + rel + dehydrobenzperidol	43	2	5
Female			
$N_2O + O_2$ + rel	42	19	3
$N_2O + O_2$ + rel + dehydrobenzperidol	47	8*	6

* $p < 0.05$

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nausea after ocular surgery We found further that female patients had more nausea and vomiting than male patients as was also pointed out by Riding (1963) Although the patients after local anaesthesia seemed to vomit less than those after N O–O relaxant anaesthesia the frequency in female patients in even this group was surprisingly high (more than 40 %) The premedication used in the present series seems to have some importance Pethidine is known to cause postoperative sickness (Bellville 1960 Dundee et al 1962) On the other hand if the postoperative vomiting after ocular surgery is mediated through the cholinergic mechanism as postulated by Anderson (in Evans & Gray 1965) the concomitant use of atropine as premedication in the present series may be of benefit in antagonizing postoperative sickness

Neurolept analgesia has been claimed to be an advantageous anaesthetic technique as far as nausea and vomiting are concerned (Edmond Seal & Prys Roberts 1970) We could not confirm this opinion in the present results al though on the other hand we found dehydrobenzperidol to be an effective anti emetic drug both after N O–O_ relaxant and after local anaesthesia in female patients The sickness must thus be caused by fentanyl which abolishes the beneficial antiemetic effect of DHBP

There was no significant difference between the various anaesthetic tech niques in ocular surgery as far as postoperative nausea and vomiting were con cerned but local anaesthesia seemed to be the most advantageous technique in this respect The antiemetic drug dehydrobenzperidol injected intramuscularly at the end of the operation reduced postoperative sickness both after N O–O relaxant anaesthesia and even more clearly after local anaesthesia

Acknowledgment

Financial support from the Silmasaatio Foundation is gratefully acknowledged

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CLIMATIC CHANGES IN THE EYES OF ESKIMOS, LAPPS AND CHEREMISSES

BY

H FORSIUS

Chronic and acute climatic changes observed in the eyes of Eskimos and USSR Cheremisses are described Chronic climatic lesions are more common in men than in women Pterygium seems to be about equally common in Eskimos and Lapps The occurrence of pinguecula was about the same in all three populations and much higher than in the urbanized Finns Band shaped climatological corneal degenerations seem to be less common and *less malignant among the Eskimo populations studied living in the* regions at latitudes 70° than among those living in the more southern regions of Labrador
In January 1970 all the Eskimos who had been driving motor sledges were observed to have acute corneal and conjunctival epithelial lesions stainable with fluorescein

Key words pinguecula – pterygium – band shaped degeneration – climatology – Eskimos – Lapps

The eye excepted all parts of the body can be covered with clothes against the cold the wind and the sun But the eyes are always unprotected For that reason the greatest changes caused by the arctic climate may be expected in and around the eyes particularly in elderly people

Based on a paper read at the Second International Symposium on Circumpolar Health Oulu Finland June 21–26 1971

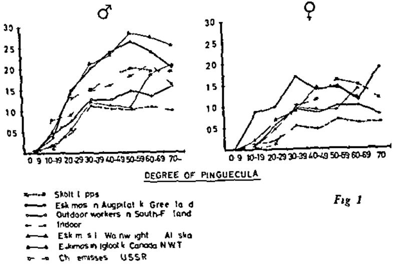


Fig 1

The circumpolar populations have long worn slit goggles as protection against ultraviolet light in the Spring This is true for Lapps Sibirian arctic populations and Eskimos But goggles become misted in severe cold and the wind and the cold of winter are therefore greater problems

The round shape of the face and the narrow interpalpebral fissure typical of the arctic rases shelter effectively against the climate These features are characteristic of the Eskimos in particular who have lived longest in the Arctic and thus have the longest history of genetic adaptation to arctic condi tions

This article describes the climatic changes observed in the eyes of Eskimos investigated during Human Adaptability expeditions (IBP/HA) to Augpilag tok Greenland in 1968 under the guidance of Dr J B Jorgensen to Wain wright Alaska 1969 under the guidance of Prof F A Milan and to Igloolik Canada in January 1971 under the guidance of Prof D Hughes In addition we have studied Lapps in Finland and Cheremisses in the Soviet Union

Chronic Changes

Pinguecula is a chronic climatic lesion of the eye which is much more con spicuous in outdoor workers We have rated this injury by degrees from zero to 3 3 meaning a very marked pinguecula zero absence of the anomaly The mean was calculated for estimates made laterally and medially of the limbus

Table I
Climatological changes in the eyes of Skolt Lapps Eskimos and Cheremisses Even small changes were noted

≧ 20 years		Band shaped corneal degeneration		Pterygium frequency		Pinguecula 1 = small 3 = large	
		No	%	No	%	No	%
Skolt Lapps	♂	91	3[illegible].2	91	8.8	109	1.[illegible]
	♀	115	20.0	115	2.6	122	1.1
Eskimos	♂	156	32.0	162	8.6	15[illegible]	1.9
	♀	165	12.7	166	1.2	161	1.1
Cheremisses USSR	♂	323	3.[illegible]	323	4.6	316	1.4

in both eyes (Forsius & Eriksson 1962) As seen from Fig 1 both the Lapps and the Eskimos have a larger pinguecula than the outdoor workers in south Finland Male Eskimos in Igloolik and female Eskimos in Augpilagtok had the most conspicuous pinguecula (Fig 1 Table I) In the aged the pinguecula becomes small again (Akimoto 1966)

The frequency of pterygium corneae was not striking in comparison with that observed in many tropic peoples (Cameron 1964) but it was high when compared with the figure of slightly over 1 per cent noted for outdoor workers in south Finland and higher than the frequency among fishermen in the Åland islands (Forsius & Eriksson 1963) Pterygium seems to be about equally common in the Eskimos and Lapps The frequency figures obtained ranges of 8–10 per cent in male The frequency of this structure was found to be markedly lower among women than men (Table I) Small changes were recorded also The climate also causes another type of corneal change This chronic photophthalmia was first described as keratitis solaris exfoliativa by Klikow (1904) in the Alps and has also been reported from Siberia and other places in the arctic Freedman (1965) described in Eskimos a band shaped degeneration of the superficial layer of the cornea at the limbus which he called Labrador keratopathy This was much more malignant than the corresponding injuries that I have seen in Lapps and later in Eskimos at northern latitudes With very few exceptions the degeneration observed in these did not extend to the

Pat No	Age	Sex	Remarks
911	36	♂	4 hours travel
58	31	♂	4 hours travel

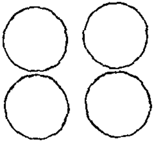


Fig 9
Fluorescein staining of the cornea after driving a motor sledge

pupillary area and thus did not affect visual acuity Among the Cheremisses *this keratopathy is very rare* (Table I) The only reasonable explanation of these differences that I can offer is that this ribbon like keratopathy is caused by ultraviolet light which obviously is much stronger in Labrador than in the regions farther north at latitudes of 70° (Forsius Eriksson & Luukka 1970 Forsius & Luukka 1971) Snowblindness is also reported to be a lesser problem in the northern parts of the arctic region than in the southern parts where the sun rises higher above the horizon e g the physicians in Upernavik NW Greenland had not seen any cases of snowblindness (1968 personal communication) However many of the Eskimos complained of irritated eyes especially in the Spring The description was not typical of snowblindness and there may be a mixture of snowblindness and acute climatological lesions of the cornea

It is interesting that a similar though nodular form of ribbon like keratitis has been observed in the desert areas around the Mediterranean (Bietti Guerra Ferraris & de Gaspare 1955 Gandolfi 1962)

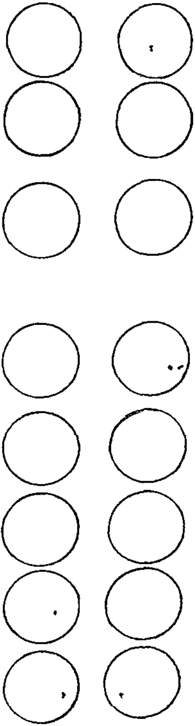
Acute Changes

Cold does not seem to cause eye lesions very easily as the modern cryo technic repeatedly has shown *In extreme climatic conditions freezing of the cornea can* occur and lead even to *permanent* lesions of the eye as described in flyers and soldiers The first report of such an instance came from Kurizin (1888) Acute lesions in Eskimos caused by snowstorms have been described by Normann Hansen (1911)

According to Kohlstad & Opsahl (1969) acute epithelial changes of the cornea stainable with Rose bengale occur in participators at ski races in severe cold In Igloolik a cold wind was blowing almost continuously in January and

Fig 8

Fluorescein staining of the cornea after a test performance consisting of driving a motor sledge for 30 min



Pat No	Age	Sex	Remarks
145	36	♂	Lid coloboma in the left eye
107	50	♂	Dots even on corneo scleral border
202	18	♂	6 hours later many new dots were seen and some earlier dots had dis appeared In the mean time he had performed outdoor work
148	38	♂	European appearance.
110	42	♂	
39	48	♂	
104	33	♂	
209	6	♂	

small particles of ice flew along the ground The mean temperature in January is between −30° and −40°C A high frequency of epithelial injuries was therefore expected in outdoor workers and hunters As seen in Figs 2 and 3 this proved true Very severe epithelial lesions stainable with fluorescein were observed in hunters and in persons who had been driving a motor sledge for experimental purposes It is interesting that the severest changes were observed in a person who showed a palpebral coloboma due to a dog bite As the eye could not be closed properly the risk of corneal injury was particularly great These corneal lesions healed within 24 hours without producing any demonstrable persistent changes They were most conspicuous centrally in the cornea but in severe cases spots stainable with fluorescein were also occasionally seen at the limbus and in the conjunctiva

The cornea was stained with fluorescein in 139 persons who came for examination In a total of 35 persons of both sexes I found superficial dots in the cornea but in the majority these dots were very few in number Twenty two of these were between the ages 10 and 29 years and had before the examination spent the time outdoors

The location in the cornea differed from that of climatic ribbon like keratitis and the cause also seems to be different namely the cold and the wind The winter temperature in Labrador where Freedman observed the more malignant form of band shaped degeneration is also much warmer than in Igloolik

It is interesting to note that the frequency of facial frostbite has risen since motor sledges were introduced (O Schaefer and J A Hildes personal communications) A person driving a dog sledge may turn his back to the direction of travel for long periods but one who drives a motor sledge must look forward all the time and the greater speed also causes a stronger head wind Protective glasses are not used in the winter in Igloolik Such changes were also seen among many Eskimos who came for the eye examination and who had been outdoors for varying periods

Two Caucasians in Igloolik who wore contact lenses showed an entirely intact cornea Perhaps contact lenses could be worn prophylactically as protection against acute epithelial changes?

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ACTA OPHTHALMOLOGICA VOL. 50 1972

From the Department of Genetics (Head Prof B Rasmuson) the Department of Paediatrics (Head Prof J W inberg) and the Department of Ophthalmolo„y (Head Prof E Linner) University of Umeå Umeå Sweden

A GENETIC STUDY OF CONGENITAL HEREDITARY MACULAR DEGENERATION IN THE COUNTY OF VÄSTERBOTTEN SWEDEN

BY

S NORDSTRÖM G HOLMGREN and W THORBURN

Two pedigrees of two separate families are presented In one of them hereditary macular degeneration was confirmed in °4 out of 43 cases examined ophthalmologically They belonged to 3 generations By means of the parish catechetical meeting examination records it has – to a rather high degree of accuracy – been possible to follow the d sease back another 4 generations to the 18th century In the other family there were 6 pa tients with congenital macular degeneration It was only possible to follow the d sease in 5 generations because of illegitimacy The mode of inheri tance in both families is autosomal dominant with high penetrance and varied expressivity

Key w rds hereditary macular degeneration – central tapetoretinal de generation – parish catechetical meeting examination records – Sweden

In 1905 Best in Germany presented a pedigree with eight cases of *congenital hereditary macular degeneration* among 59 cases examined Since then several other pedigrees have been presented in European as well as in American litera

Based on a paper read at the Second Internat onal Symposium on Circumpolar Health O lu Finlan l June °1–°6 1971

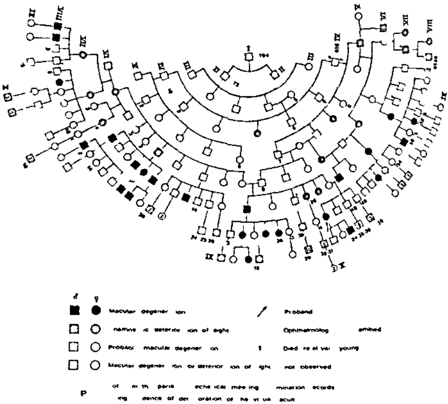


Fig 1
Pedigree 1 First family

ture (Falls 1949–50 Braley & Spivey 1964) In Sweden a survey was made in 1961 by Dr Yngve Barkman who examined a big family in the county of Dalecarlia Barkman calls the disease *central tapetoretinal degeneration* (Barkman 1961)

The disease gives a somewhat varied picture but is characterized by a degeneration of the retina in macula lutea often resulting in a rapid and radical deterioration of the visual acuity Ophthalmological examination reveals spots of lighter pigmentation as a rule with a very irregular border Sometimes such changes in the retina are observed before any deterioration of the visual acuity is noticed by the patient

In this paper a survey of two families in the county of Vasterbotten will be presented (Figs 1 and 2) In the first family (Fig 1) 43 patients were examined ophthalmologically The disease has been diagnosed in 24 of them Closer examination of still more members of the younger generations would probably reveal further cases Many of these patients are still so young that deterioration

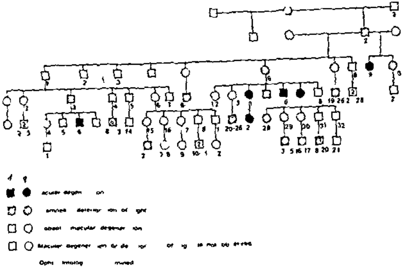


Fig 2
Pedigree 2 Second family

of the visual acuity has not yet begun in spite of the fact that they may suffer from the disease The age of onset varies from a few years to over 30 years of age (Barkman 1961 Braley & Spivey 1964) Patients with an anamnestic deterioration of sight have probably had a macular degeneration Patients VII 30 and VIII 31 (Fig 1) however are exceptions because of other ocular diseases

As it is impossible to get back to earlier generations though diagnoses made by physicians we have used another method to trace the disease in the ancestors In Sweden we have a unique material which has been used for this purpose the *parish catechetical meeting examination records* In these records it is possible to find judgments passed on the parishioners ability to read from a primer a Bible a catechism and family sermons The judgments were passed in connection with an examination performed by the clergyman at regular parish catechetical meetings The records were made with great care The judgments were marked with different symbols those from the 19th century corresponding to a 5 degree scale from degree 1 – has started to read to degree 5 – full ability of reading (Johansson 1969)

As this disease strongly affects the visual acuity and consequently the ability to read this ought in some way or other to appear in the above mentioned records That is the case with all persons in the pedigree marked P (Fig 1)

They have very bad marks in reading and in some cases there are also notes in the margin e g weak eyed With all probability the disease can be traced back to the woman III 5 (Fig 1)

Some of the members of the second family (Fig 2) came from the same village as members of the first one It therefore seems possible that the families could have a common origin Further investigations backwards in this family were very difficult The man II 2 (Fig 2), born in the middle of the 19th century had poor eyesight and had in two marriages fathered children with bad visual acuity Hereditary macular degeneration has since been confirmed among his descendants It was not possible to trace this pedigree any further backwards because of illegitimacy

As a result of the two pedigrees it is evident that the disease is caused by an autosomal dominant mutant

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EYE DISEASE IN THE ESKIMO AND IN THE AUSTRALIAN ABORIGINAL A BRIEF COMPARISON

BY

IDA MANN

Two groups of persons living under very different conditions of environ ment and culture were studied from the point of view of their eye diseases The Eskimos of the north of the American Continent are contrasted in this context with the Australian Aboriginals
The first group culturally adapted to extreme cold and largely isolated until recently shows a high incidence of phlyctenulosis and the results of trauma Strabismus narrow angle glaucoma and senile cataract were found *inter alia* Trachoma leprosy and nutritional eye disease were absent
The Australian Aboriginals live in a dry tropical climate They are highly subject to trachoma leprosy and some cataract. Glaucoma con vergent strabismus and nutritional eye d sease were absent.
In both groups the diet is high in animal protein Both groups are no longer isolated and the disease pattern is changing

Key words Australian Aboriginals – culture and climate – Eskimos – glaucoma – nutritional disease – trachoma

Those of us who have worked in varied regions of the world are fully aware of the climatic, historic racial and cultural factors which can influence the type of eye disease found

Based on a paper read at the Second International Symposium on Circumpolar Health Oulo June 21–26 1971

In the Arctic regions the effect of cold is all important in determining the life style The history of contacts with other races may help to decide the type of infectious disease found The Alaskan Eskimo for example is free of trachoma while this disease is common in the peoples of the Russian Arctic who were in contact early with the great transcontinental routes of trade from North Africa The Eskimos however were exposed to tuberculosis and its spread was fostered by their way of life dictated by climate

In the Tropics there are various diseases dependent on a vector or an inter mediate host whose life also is largely determined by climate Such conditions as the onchocerciasis of Central Africa could not exist in the arctic since the vector the Simulium fly needs flowing water and a tropical temperature

The isolation of small groups will also foster the spread of genetic conditions An example is seen in the high percentage of achromats in the Danish island of Fur (Franceshetti 1960) and of cases of Norrie s disease in Bornholm (Warburg 1961)

Historic accidents may determine disease distribution such as the spread of favism to South east Europe through migration of Jews from Baghdad or better known the spread of trachoma along trade routes from the Nile Valley

Life expectancy will influence the prevalence of degenerative diseases e g cataract and senile macular degeneration which are rare in primitive societies and increase with a rising standard of living though they may well have a genetic basis

Isolated groups are of interest because of the contrasts often found between them We propose to deal with two examples the Alaskan Eskimos and the Australian Aboriginals Both groups live tough and somewhat dangerous lives and both have met with expanding European culture within comparatively recent times often to their detriment

Table I shows similarities and contrasts between the two groups

Dr Milo Fritz analysed the records of 39 019 Eskimo patients treated at the Alaskan Native Service Hospital Anchorage between 1953 and 1970 These Eskimos have been isolated from European influence for centuries until recent ly The first contacts were probably Russian Mixing with Amerind tribes was probably slight as there is hostility between the two groups and therefore some inbreeding of Eskimo may have taken place On the other hand in recent years there has been definite mixing with European blood

Fritz survey showed that phlyctenulosis was the most frequent eye disease and was almost always associated with either pulmonary tuberculosis or chronic middle ear disease or suppurative mastoiditis or both It led to much corneal scarring in the past but is slowly being brought under control by improved medical services Tuberculosis spread was and is undoubtedly mediated by

Table I

	Eskimos	*Australian Aboriginals*
Racial Stock	Mongolian from North east Asia but few full bloods	Proto Caucasian from South east Asia Many full bloods
Environment	Extreme cold Extreme variations in hours of daylight between winter and summer	Approximately steady dry tropical climate with wet and dry seasons Little alteration in length of daylight
Diet	Fish whale and seal meat – high protein	Kangaroo lizard and other reptiles Now beef and mutton. High protein.
Culture	Gradual assumption of European habits but still largely conditioned by climatic limitations Hunting fishing preparation of furs and skins Beginning interest in industry Agriculture not possible	Nomadic hunting existence gradually being transformed into settlement life and herding No interest in agriculture.
Most Prevalent Eye Diseases	Phlyctenulosis++ Trauma tropias (strabismus) Senile cataract some pterygia Narrow angle glaucoma Senile macular degeneration No trachoma No leprosy No nutritional disease	Trachoma++ leprosy pterygium++ very little cataract No glaucoma. No convergent strabismus No nutritional disease

the close crowding together of families at night owing to the intense cold It is therefore of climatic origin Phlyctenulosis was noted in 457 instances

The expectation of life of the Eskimos is 64 4 years for those who survive the first year of life in the rest of the U S A it is 70 6 years If infant deaths which are about twice the U S A national average are included the life expectancy of Eskimos falls to 34.5 years (In the U S A this would be 66 years) We would expect therefore to find only a certain number of degenerative conditions due to age Fritz (1970) in an analysis of 1 889 internal eye diseases reported as follows

Senile cataract	=	266 cases
Glaucoma	=	98 cases
Senile macular degeneration	=	23 cases

Trauma accounts for a large *percentage of hospital admissions* 343 cases of eye injury were found by Fritz (1970) They are increasing with the introduction of more mechanical aids such as snow machines Construction work accounts for many eye injuries and *it is to be noted that instruction in the use* of safety precautions has not caught up with *progress in using* tools Injuries from fighting (personal) wife beating bashing when under the influence of alcohol etc are also relatively common

Certain diseases are relatively unknown in the Arctic for example trachoma and toxoplasmosis The reason for the absence of trachoma is not as one might first expect due to the effect of the harsh climate on the organism Trachoma is widespread in Siberia which is just as cold and where intensive campaigns for its suppression are in progress Toxoplasmosis also occurs in Russia I know of no reason why the toxoplasma is rare or absent in Alaska

Both Dr Fritz and Dr Elizabeth Cass have noted the increase in myopia among Eskimos Myopia is now generally considered to have a hereditary basis and therefore it might appear strange that it has only recently become a problem in Eskimos However in his talk in Yellowknife in 1970 Fritz pointed out that succeeding waves of youthful members of the Armed Forces young construction workers and adventurous young men since the beginning of the century make the presence of even one full blooded Eskimo Indian or Aleut today extremely unlikely

Let us now contrast this Eskimo picture with that of the tribal Australian Aboriginal These people live in the dry tropics within a few degrees *of the* Equator They are now partially acculturated to the white Australian way of life but their disease pattern has not changed much Their environment is a hot dry *dusty partial desert with very little water and a low rainfall* in the wet season Their personal hygiene is very poor Many surveys of them and their diseases have been done during the past fifteen or more years Among nomads and semi nomads trachoma is by far the commonest eye disease Its incidence varies from 50 % to 75 % of the total population Infection occurs in the first year of life In most instances especially in fully nomadic groups and in other groups that have received treatment the outcome is comforting the majority healing before the age of 20 with little or no impairment of sight

In an analysis of 1 947 cases of eye disease surveyed by me in the north of Western Australia trachoma showed an incidence of 61 58 % (1 199 cases) The next highest incidence was that of pterygium 6 % (118 cases) The exposure *to* intense ultra violet light in the dry tropics would seem to account for *this* as pterygium is well known in both Aboriginal and white persons in Western Australia It is not *common in Eskimos* who *for centuries* have known the necessity for protection and have evolved a very efficient wooden eye guard

Ocular leprosy (2 %) is another condition not found is Eskimos Its occurrence is due to historic accident as leprosy was introduced into the north of Western Australia by Chinese and other Asiatic immigrants probably several centuries ago and has never been seen in Alaska

The incidence of senile cataract (3 34 %) in Aboriginals is less than in Eskimos (14 %) and in white Australians (7 % in a survey of 6 410 eye diseases in Perth W A) though the expectation of life is not very different in Eskimos and white Australians We have no accurate life statistics for Aboriginals

Glaucoma is of interest Ninety eight (19 %) cases were found in Eskimos mostly narrow angle while in Australian Aboriginals the incidence is less than 1 % of all eye diseases and the few patients found may not have been full bloods

Phlyctenulosis in tropical W A was also rare being found in less than 1 % of all patients Pulmonary tuberculosis is rare Natives always sleep in the open air and not often in close contact with each other

Industrial eye injury is of course absent among tribal Australian Aboriginals though a few cases of trauma from accidents were found (less than 1 %)

Convergent strabismus and amblyopia ex anopsia are rare or absent in Aboriginals In 1 889 Eskimo 214 cases of esotropia were found This would seem to imply a genetic basis for the tropias as is often found to be the case in white persons in Australia In a survey of 6 410 white patients in Perth in 1966 5?9 cases of strabismus were found

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Discussion

The pictures of eye disease in these contrasting cultures are as diverse as are the circumstances in which they occur On the one hand (Eskimos) we have environmentally intense cold leading to overcrowding and imperfect sanitation recently introduced industry and geographic and historic isolation Phlyctenulosis and trauma head the list but many infections are absent (e g trachoma) Senile degenerations occur in proportion to expectation of life in both groups Narrow angle glaucoma occurs

The Australian Aborigina on the other hand is subjected to heat and drought He has had contact with other races for much longer than the Eskimos but there has been relatively little interbreeding His problem is infection from trachoma and leprosy Glaucoma of all forms is absent or extremely rare

Both groups in their native conditions are free of nutritional eye disease Both groups are largely carnivorous

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TREATMENT OF TRAUMATIC HYPHAEMA WITH CORTICOSTEROIDS AND MYDRIATICS

BY

ARNE ÖHRSTRÖM

The incidence of secondary haemorrhage following contusion of the eye in a 9 year series (356 cases) in which patients who had hyphaema were treated locally with corticosteroids and mydriatics was found to be 2 4 %. This figure appears to be the lowest on record

Key words hyphaema – eye contusion – accident – thrombolysis

During the last 9 years treatment of ocular contusions at the eye clinic has consisted mainly of the instillation of mydriatics and corticosteroids. This paper concerns a retrospective study of the results of this treatment

Material

The records of all patients treated because of contusion of the eye between 1963 and the end of 1971 were examined. Cases with coexisting perforating injuries were not accepted

Rece ed June 26 19

Methods

Since all the patients had been admitted as emergencies at all hours of the day and since they therefore had been seen by a wide variety of physicians who happened to be on duty, the notes in the patients records had not been made in a uniform way with the result that it was occasionally difficult to judge the nature of the injury from the patients hospital charts The records were examined for symptoms and complications during hospitalisation and for later sequelae (see Table I) Only symptoms clearly described in the records were accepted as such This means that the frequency of symptoms given in the Table should be regarded as a minimum frequency In some cases in which massive hyphaema had made it impossible to examine the interior of the eye at admission notes were made of those symptoms and signs that were obviously ascribable to the contusion and still demonstrable after clearing of the anterior chamber The time of onset and type of therapy given were noted The material was then divided into two groups one with and one without hyphaema and the former group was studied Not all of the patients were admitted on the same day as the accident and treatment with corticosteroids was sometimes postponed a day or so because of corneal erosions for example

Owing to this delay contusions with hyphaema not treated within two days of the accident were not included in the calculation of the incidence of secondary haemorrhage in the present investigation The assumption was that the treatment thus had had enough time to be effective This was because the risk of secondary bleeding is considered to be greatest on the 3rd–4th day To judge the effect of treatment it was decided to study a relatively uniform group in which treatment had been started within two days of the injury

Contusions of the eye without hyphaema were of course not included in the calculations

Treatment

Bed rest for 3–4 days and bandaging of the injured eye only As a mydriatic 1 % atropine was applied 1–3 times a day and as a corticosteroid 2.5 % cortisonacetate (Cortone Merck Sharp & Dohme) and from the beginning of 1965 0.1 % fluormethylprednisolone (Isopto Maxidex Alcon) was given 3–5 times a day A few cases with severe corneal erosion were treated topically with combined antibiotics and corticosteroids and of course mydriatics The intraocular pressure was not regularly measured on admission When the

Table I
Associated lesions symptoms and complications

	All contusions	Contusions with hyphaema	The selected group with hyphaema
Hyphaema	184	184	167
Pupil changes	193	130	120
Iridodialysis	7	6	5
Dislocation of lens	4	2	2
Vitreous retinal haemorrhage	62	22	19
Choroidal rupture	13	7	5
Secondary iritis	4	4	3
Blood stained cornea	1	1	0
Retinal detachment	3	1	1
Glaucoma	3	2	2
Permanent reduction of visual acuity	91	15	12
Secondary haemorrhage	4	4	4
Number of patients	356	184	167

tension increased the patient was treated with acetazolamide in a dose of up to 500–100 mg per day Surgery was never resorted to for evacuation of blood or a clot or to a reduce intraocular pressure

Results

The symptoms on admission complications and the results of treatment are given in Table 1 Secondary hyphaema occurred in 4 cases Of the 356 cases 184 had a hyphaema and 167 cases filled the criteria for acceptance in the selected group to which the four secondary haemorrhages all belonged In 3 patients with secondary *haemorrhage* the haemorrhage had been preceded by secondary iritis In all 4 cases the course after secondary haemorrhage was uncomplicated and the eye recovered its *original function* without any sequelae caused by the secondary bleeding a remarkably benign course

Case Reports

A 10 year old boy had massive hyphaema preventing inspection of the interior of the eye. On admission the intraocular pressure was palpably increased. The patient was treated with 0.1 % fluormethylprednisolone × 5 and 1 % atropine × 1. Five days later there was a secondary haemorrhage which was however absorbed without further complications. After the eye had cleared, a rupture of the sphincter was seen in the iris as well as a choroidal rupture extending partly through the maculae with subsequent reduction of vision to 0.1–0.2. No further sequelae were seen during the following 4 years.

A 12 year old boy was admitted to hospital one day after the accident with small rests of blood on Descemet's membrane and an aqueous flare of red corpuscles. No other symptoms. Treated with 1 % atropine × 1 and 0.1 % fluormethylprednisolone × 3. Secondary haemorrhage 4 days later but no later complications. No sequelae were found at last review 3 months later.

A 17 year old boy with massive hyphaema preventing inspection of the interior of the eye. Two days after admission the eye suddenly became painful and the whole anterior chamber was again filled with blood. The intraocular pressure was increased. The patient was treated first with 0.2 % scopolamine × 3 and 0.5 % prednisolone acetate with sulphacetamide sodium (Metimyd, Schering Corp.) and after the secondary haemorrhage with acetazolamide 250 mg × 3 and an injection of 40 I.U. ACTH once a day for 3 days. No further complications. At discharge he had iridodialysis, some small preretinal haemorrhages, a choroidal rupture and moderate oedema of the macula. When last seen 3 months later both vision and tension were normal.

A 20 year old man with 3 mm hyphaema on admission. Moderate corneal erosion. Treated with 1 % atropine × 1 and 0.5 % prednisolone acetate with sulphacetamide sodium × 5. Three days later he had a secondary haemorrhage but the further course was uneventful.

The only patient with a blood stained cornea was a 19 year old man who was not admitted to hospital until 3 days after the accident and was therefore not included in the selected group. On admission the entire anterior chamber was filled with blood and the intraocular pressure was increased. No secondary bleeding could be demonstrated but the cornea was blood stained and the eye finally went into phthisis.

In 21 cases visual acuity was permanently reduced because of degeneration of the macula in 13, opacities of the lens in 2, secondary glaucoma in 2, choroidal scar in 1, deformed pupil in 1, retinal detachment in a female with severe myopia in 1, and a blood stained cornea with phthisis in 1.

Age and sex distribution

See Table II. As expected, males were more common and the incidence was highest in both sexes between the ages of 10 and 19 years.

Table II
Age and sex of the patients

Age	Males	Females
0–9	59	7
10–19	122	27
20–29	54	7
30–39	33	4
40–49	27	2
50–	25	1

Discussion

Secondary haemorrhage occurred in 4 (2.4 %) of 167 patients with primary hyphaema treated with corticosteroids and mydriatics within 2 days of the accident. This is one of the lowest incidences on record.

Gregersen (1962) and Geeraets (1966) used strictly conservative therapy and reported an incidence of secondary haemorrhage of 5 % and 6.6 % respectively. Somewhat less encouraging results have been reported by Thygesson (1952) 38 %, Shea (1951) 14 %, Kushner (1959) 16 %, Morris (1960) 17 %, Cole (1964) 31 %, Britten (1965) 11 % and Howard (1965) 10 %.

Oksala (1967) used corticosteroids and mydriatics locally in the treatment of traumatic hyphaema but not routinely and the incidence of secondary haemorrhage in his series was 10 %. Also Zetterstrom (1969) reported the use of mydriatics and corticosteroids but said nothing about the incidence of primary hyphaema; the cases of contusion were all unselected and only half of the 133 cases were treated with mydriatics and steroids, the other half receiving conservative treatment. All secondary haemorrhages occurred in the group treated conservatively.

POSSIBLE CAUSES OF SECONDARY HAEMORRHAGE

Laceration of the vessels by the contusion is immediately followed by vaso constriction and subsequent formation of clots plugging the injured vessels. Increased fibrinolysis may cause digestion of the clot with the secondary

haemorrhage as a result The traumatic inflammation increases the permeability of the blood aqueous barrier and permits the passage of plasma proteins into the anterior chamber The globulin plasminogen can thus enter the anterior chamber and be activated to plasmin, the main fibrinolytic enzyme A reduced inflow of plasma proteins including plasminogen should consequently reduce that part of the fibrinolytic activity in the anterior chamber that is due to an abnormal passage of plasminogen from plasma to the anterior chamber The corticosteroids have an inhibiting effect on fibrinolysis as well as an anti inflammatory and membrane stabilizing effect Corticosteroid therapy will normalize the damaged blood aqueous barrier and thus reduce the leakage of plasma proteins to the aqueous humor Atropine immobilises the iris and the ciliary body which are the most common sites of rupture and thereby immobilises the affected area with the vessels plugged by clots until the latter are organised and firm

Treatment with corticosteroids and mydriatics did not produce any side effects in the present material Judging from the good results obtained the method compares favourably with the many alternative procedures used in the treatment of hyphaema

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Case Reports

Case 1

S E a 43-year old man was admitted to hospital in July 1969 because of sudden visual loss in the left eye Diabetes had been diagnosed six years previously but its recent control had been poor Ocular examination showed a visual acuity of 6 6 in the ri ht eye with a normal visual field A few retinal microaneurysms were detected in the posterior pole Visual acuity in the left eye was u/30 and examination of the visual field revealed enlargement of the blind spot and a relative central scotoma to red Examination of the fundus showed an optic disc with marked hyper aemia and oedema and a few haemorrhages in the lower nasal quadrant

Five months later in December 1969 the patient returned to hospital because of sudden loss of vision in the right eye On examination, the visual acuity of the right eye was 6.30 and there was enlargement of the blind spot and congestion and oedema of the optic disc were observed (Fig 1) Fluorescein angiography showed marked capillary dilatation microaneurysms and early extravasation of the dye in the region of the optic disc (Fig 2 A) followed by residual fluorescence particularly in the vertical plane (Fig 2 B) The visual acuity of the left eye was 6'30 and there was a nasal inferior wedge shaped field defect with mild secondary atrophy of the optic disc and sheathing of arteries

Neurological examination revealed loss of patellar reflexes and diminution of deep sensation in both legs The skull films lumbar puncture brain scan and electro encephalography showed no abnormalities Treatment with ACTH did not result in any improvement. The diabetes was controlled with 40 units of regular insulin and 8 units of Protamine Zinc insulin daily

Case 2

Z A a 46 year old man was first examined in September 1970 because of blurring of vis on in the left eye Ocular examination revealed visual acuity of 6/6 in the

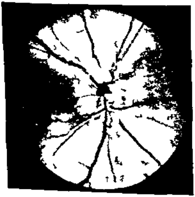


Fig 1

Ca e 1 Fundus photograph showing oedema of the right optic d sc

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OPTIC NERVE INVOLVEMENT IN DIABETES

BY

L. YANKO U TICHO and M IVRY

Six patients with unilateral or bilateral neuritis and uncontrolled diabetes mellitus are reported In addition the pathogenesis of optic nerve involvement in diabetes mellitus is reviewed It is suggested that diabetic optic neuropathy may be the result of a capillary disorder in the superficial optic disc area similar to the capillary changes found in diabetic retinopathy

Key words optic nerve – diabetes mellitus

The incidence of optic nerve involvement in diabetic patients varies according to different authors Foster Moore (1920) described six cases among 61 diabetics and Skillern & Lockhard (1959) reported 14 cases in older patients with uncontrolled diabetes However Topilow & Bisland (1952) and Freund et al (1965) describe optic nerve involvement as a rare complication of diabetes

Whatever the true incidence is each individual case of acute diabetic optic neuritis presents a problem particularly because so little is known about the mode of optic nerve involvement in this metabolic disorder Recently we have observed six cases of acute optic neuritis in patients with uncontrolled diabetes These cases serve as the basis for a review of the pathogenesis of optic nerve involvement in diabetes

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Neurological examination showed no abnormalities and laboratory investigations disclosed a fasting blood sugar of 171 mg % and postprandial glycosuria The patient was treated with Diabinese and also received corticosteroids for his optic nerve condition

Four months later in January 1971 the patient complained of blurring of vision in the right eye Examination showed a visual acuity of 6/21 in the right eye with concentric contraction in the visual field more advanced in the lower altitudinal field Fundal examination disclosed a congestive form of oedema of the optic disc with a few haemorrhages in the lower temporal area (Fig 3) Fluorescein angiography showed slight dilatation of the capillary network of the lower temporal disc with extension beyond its border (Fig 4) Fluorescein first leaked into the temporal area and later diffusely over the disc The visual acuity in the left eye was 6/15 and there was a concentric contraction of the visual field which was more advanced in the lower altitudinal field The fundus showed mild atrophy of the optic disc Systemic steroid therapy resulted in slight improvement of the visual acuity and visual fields

Case 3

C B a 45 year old man was first examined in February 1971 because of visual loss in the left eye of one year's duration Diabetes had been diagnosed 2 years previously but recent diabetic control was poor

Ocular examination showed a visual acuity of CF 2 m in the right eye and a non proliferative diabetic retinopathy with hyperaemia and oedema of the optic disc Visual acuity in the left eye was 6/30 and extensive non proliferative diabetic retinal changes were present with a normal optic disc Visual fields could not be charted Neurological examination revealed no pathological changes

Case 4

B G a 53 year old woman was first seen in December 1969 because of sudden

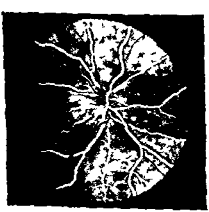


Fig 4

Fluorescein angiogram of right eye in case 2 Early venous phase showing slight dilatation of capillary network of the lower temporal disc

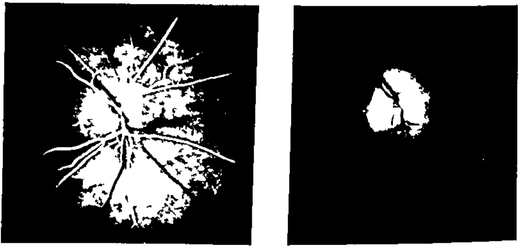


Fig 2 A, B

Fluorescein angiograms of right eye from case 1 showing (A) Early venous phase with capillary dilatation microaneurysms and extravasation of dye in the area of the optic disc (B) Late phase with residual fluorescence extending beyond the optic disc border

right eye and a normal fundus and visual field Visual acuity in the left eye was 6/9 and there was a concentric contraction of the visual field which was more advanced in the lower nasal field Fundal examination showed hyperaemia and oedema of the optic disc with a few haemorrhages in the lower temporal quadrant Fluorescein angiography revealed a few microaneurysms in the macular area There was an increase in the number of capillaries in the lower part of the optic disc with leakage of dye in the early venous phase

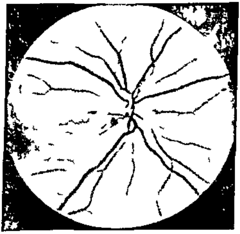


Fig 3

Case 2 Photograph of right fundus showing oedema of the optic disc with a few haemorrhages in the lower temporal area

Neurological examination showed no abnormalities and laboratory investigations disclosed a fasting blood sugar of 1,1 mg % and postprandial glycosuria The patient was treated with Diabinese and also received corticosteroids for his optic nerve condition

Four months later in January 1971 the patient complained of blurring of vision in the right eye Examination showed a visual acuity of 6/21 in the right eye with concentric contraction in the visual field more advanced in the lower altitudinal field Fundal examination disclosed a congestive form of oedema of the optic disc with a few haemorrhages in the lower temporal area (Fig 3) Fluorescein angiography showed slight dilatation of the capillary network of the lower temporal disc with extension beyond its border (Fig 4) Fluorescein first leaked into the temporal area and later diffusely over the disc The visual acuity in the left eye was 6/15 and there was a concentric contraction of the visual field which was more advanced in the lower altitudinal field The fundus showed mild atrophy of the optic disc Systemic steroid therapy resulted in slight improvement of the visual acuity and visual fields

Case 3

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Case 4

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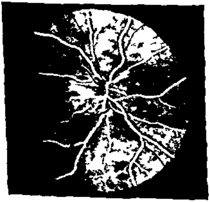


Fig 4

Fluorescein angiogram of right eye in case ? Early venous phase showing slight d latation of capillary network of the lower temporal disc

visual loss in the right eye Diabetes had been diagnosed 12 years earlier but recent diabetic control was poor

Ocular examination revealed a visual acuity of CF 1 5 m in the right eye non proliferative diabetic retinopathy and a congestive form of oedema of the optic disc There were a central scotoma and a concentric contraction of the visual field. The visual acuity in the left eye was 6/12 with a non proliferative form of diabetic retinopathy and a normal optic disc and visual field Neurological examination revealed a loss of patellar and Achilles tendon reflexes

Three months later ocular examination of the right eye showed an improvement of the visual acuity to 6/30 and pallor of the optic disc

Case 5

S S a 53 year old woman was first examined in July 1970 because of visual loss in the left eye Diabetes had been diagnosed 8 months previously but its control had been poor

Ocular examination showed a visual acuity of 6/9 in the right eye and a non proliferative form of diabetic retinopathy with a normal optic disc Visual acuity in the left eye was 6/21 and fundal examination revealed a non proliferative form of diabetic retinopathy with a hyperaemic and oedematous optic disc Visual fields could not be tested

Neurological examination revealed a loss of patellar and Achilles tendon reflexes The skull films brain scan and electroencephalography were all within normal limits

Case 6

K Z a 60 year old man was first seen in September 1971 because of sudden loss of vision in the right eye

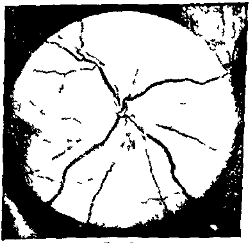


Fig 5

Case 6 Photograph of right fundus showing oedema of the optic disc

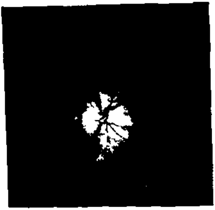


Fig 6

Fluorescein angiogram of right eye in case 6 Late phase showing residual fluorescence extending beyond the optic disc border

Ocular examination showed a visual acuity of 6/60 in the right eye Examination of the visual field revealed an enlargement of the blind spot and contraction of the lower nasal field The optic disc showed hyperaemia and oedema (Fig 5) and no signs of diabetic retinopathy were found Fluorescein angiography disclosed dilatation of the capillary network on the disc extending beyond its borders Marked leakage already appeared in the early venous phase which partially concealed the large vessels Staining persisted for more than one hour and expanded in all directions (Fig 6) Visual acuity in the left eye was 6/9 and the fundus and visual field were normal

Laboratory investigation revealed a fasting blood sugar of 280 mg % and post prandial glycosuria Neurological examination including skull films and electroencephalography showed no abnormalities

Treatment with anti diabetic drugs (Orsinon) and Dexasone resulted in a slight improvement in the visual acuity to 6/36 and in the visual field

Six months later the patient was hospitalized again because of a sudden deterioration in visual acuity in his left eye to 6/24 The optic disc showed marked oedema and a few flame shaped haemorrhages were present on its lower and temporal border Visual acuity in the right eye was 6/36 and there was pallor of the optic disc more marked in the temporal area

Discussion

The six patients reported showed a sudden deterioration in visual acuity in the affected eye associated with congestive oedema of the optic disc In three patients both optic nerves were involved with initial involvement of one eye followed by involvement of the other eye within 6 months The optic neuritis

observed was painless and of an intrabulbar type Three cases showed an associated bilateral non proliferative diabetic retinopathy whereas the other three patients had no retinopathy or only a few retinal microaneurysms Three cases were associated with peripheral nerve involvement It is of interest to note that all the patients were on a poor diabetic control for an unknown period of time prior to the onset of symptoms and two of them were not aware of having diabetes before examination

Ocular complications of diabetes have been described in detail however few reports deal with optic nerve involvement in this metabolic disease The clinical diagnosis of diabetic optic neuritis is always tentative to some extent and there are no cases where its presence has been confidently proven Never theless it has been suggested that optic nerve involvement is a specific compli cation of diabetes (Kestenbaum 1961 Walsh & Hoyt 1969) but its nature and pathogenesis are still uncertain

Skillern & Lockhard (1959) attributed the optic nerve involvement to toxic metabolic changes affecting patients with long standing or severe uncontrolled diabetes Few reports (Freund et al 1965 Cogan 1966) suggest a causal rela tionship of diabetic optic neuritis with peripheral neuropathy To what extent this comparison helps to elucidate the pathogenesis of diabetic optic neuritis has not yet been established Observations on isolated peripheral nerve fibres from patients with diabetic neuropathy (Thomas & Lascelles 1965) showed that there was segmental demyelination and remyelination suggesting that the neuropathy may result from a disturbance of Schwann cell metabolism In addition recent studies (Gabbay 1966 Gabbay & Snider 1970 Gabbay 1971) have suggested that the sorbitol pathway of glucose metabolism may play an important role in the etiology of diabetic neuropathy Aldose reductase and polyol dehydrogenase two enzymes of the sorbitol pathway have been dem onstrated in the Schwann cell of the peripheral nerve in spinal cord and in brain tissue of rats (Gabbay 1966 Stewart et al 1967) These enzymes are not fully saturated at normal blood glucose levels but increase their activity in response to an increase in glucose concentration Thus accumulation of sorbital in the nerve is dependent on an increase in blood sugar and it is possible that this is related to neuropathy or disorders of the optic nerve in diabetes

On the other hand others (Miller & Smith 1966 Lubow & Makley 1971) have suggested that optic nerve involvement in diabetes is due to a vascular phenomenon related to occlusion of the optic nerve nutrients Lubow & Makley (1971) claim that it is an ischaemic manifestation of diabetic microangiopathy following acute vascular insufficiency in the absence of adequate collateral circulation within the optic papilla Ischaemic optic neuropathy due to infarc

tion of the optic nerve (Miller & Smith 1966) is a well known complication of some systemic vascular diseases and is probably most commonly encountered in atherosclerosis (François 1962) and giant cell arteritis (Cullen 1967) This syndrome as described by Miller & Smith (1966) and Ellenberger & Netsky (1968) consists of a sudden onset of visual field defects particularly of a large fibre bundle type or altitudinal haemianopsia associated with transient pallor and swelling of the optic disc

Freund et al (1966) have assumed that diabetic optic nerve involvement is due to diffuse vascular changes and an intermediate factor between the com plex metabolic changes in diabetes and the neurological complications

It is also possible that the optic nerve involvement in diabetes is the result of capillary changes in the superficial optic disc similar to changes found elsewhere in the retina as part of the picture of diabetic retinopathy In this context it is of interest to recall the work of Hayreh (1936) who described a capillary network in the optic nerve head derived from branches of the retinal arterioles and most commonly from recurrent branches of the vessels in the circumpapillary region The clinical features observed in our diabetic patients were an expression of functional impairment of the optic nerve with angio graphic evidence of capillary involvement in the optic disc area The function of the blood flow through the capillaries is maintenance of vital nutrition and removal of metabolic products from the optic nerve fibres so that a lack of perfusion or functional abnormalities of capillary wall can be expected to result in deterioration of vision

All our diabetic patients were poorly controlled for an unknown period of time prior to onset of their symptoms and this may bear some relation to the pathogenesis of optic neuritis in diabetes It is known that the main component of the basement membrane of small blood vessels is a carbohydrate containing protein of collagenous type (Spiro 1967) Accordingly synthesis or breakdown of the protein is probably most sensitive to some of the metabolic disturbances encountered in diabetes (Caird et al 1969) Thus increased synthesis or de creased breakdown of this protein may result from metabolic disturbances of diabetes and the extent of altered protein status may be related to the degree of metabolic disturbance If this reasoning is valid a relationship between the control of diabetes and the frequency of microangiopathy may be envisaged

The pathogenesis of optic nerve involvement in diabetes is still unclear however the above hypothesis suggests that diabetic optic neuropathy may be a consequence of a capillary disorder in the optic disc area analogous to that occurring elsewhere in the retina in diabetes

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A NEW CHART FOR TESTING LINE ACUITY IN AMBLYOPIA

BY

VEIKKO TOMMILA

A test chart in which each row contains an equal number of E letters has been used for testing the so called line acuity in amblyopia patients under pleoptic treatment. The distances between symbols and the spaces between rows change in relation to letter size and the positions of the E letters can be varied so as to make memorising of the chart impossible
The visual acuity of 84 amblyopia patients under pleoptic treatment has been tested with this chart with the ordinary Snellen type test chart and with single E-letters before and after therapy The study shows that the deeper the amblyopia the greater are the differences in the results obtained with the three charts Single E acuity can be as much as five times better than line acuity The differences in results yielded by Snellen chart and by the line chart are significant in the case of deep amblyopia Separation difficulty increases at the beginning of treatment This chart appears to be well suited to daily testing of line acuity during pleoptic treatment The importance of the separation difficulty in the vision screening studies for amblyopia has been stressed

Key words visual acuity – amblyopia – testing chart.

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One of the characteristics of amblyopia is the so called separation difficulty, i. e. the crowding phenomenon which refers to the ability to see isolated symbols better than grouped symbols. It has been shown that the phenomenon, however, is not restricted to amblyopia but is quite common (Ehlers 1953, Adler 1959, Thomas Decortis 1959) and is quantitatively related to the level of visual acuity (Stuart & Burian 1962).

The separation difficulty of an eye with normal vision is small, in other words it sees grouped letters almost equally as well as isolated ones (Stuart & Burian 1962). The treatment of amblyopia has therefore been considered to be successful only when the ability of the treated eye to see grouped letters, so called line acuity, has been normalised.

When the improvement of vision is followed during pleoptic treatment, especially at the beginning of treatment, the visual acuities of deeply amblyopic eyes are examined. Rapid improvement of vision can often be verified by using separate symbols. It is difficult to follow the development of line acuity as an ordinary test chart (to be called below the Snellen chart) for various reasons is not suitable for the daily examination of line acuity. In the first place ordinary test charts generally contain only 1 or 2 letters for the testing of low acuity values. Hence it is principally single acuity which is examined for deep amblyopia and principally line acuity for milder amblyopias. Secondly, the relative distances between the symbols vary on different rows. The distances between the rows also vary. A further disadvantage is that, as the chart contains only a few large letters, it is easy to memorise and hence daily testing with the same chart is not possible.

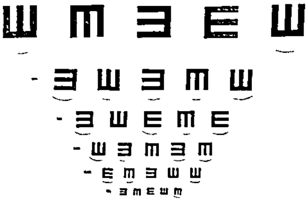


Fig 1

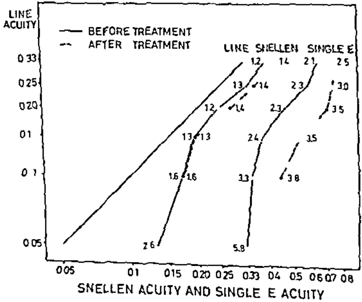
Test chart for the examination of line acuity

To obviate these drawbacks the author has begun to use for the examination of line acuity a test chart in which there are equally many E letters on each row The distances between them and between the rows vary in geometrical ratio to the size of the letters In addition the E s can be rotated to different positions so that the chart is impossible to memorise It contains lines 0 1–0.5 The testing distance is 5 m A visual acuity of 0 05 is obtained by examining line 0 1 from a distance of 2 5 metres The chart is illuminated from outside (Fig 1)

The suitability of the chart for testing of line acuity was studied by comparing the results obtained using it with those given by the Snellen chart and separate E s

Material

Eighty four patients with strabismus or anisometropia amblyopia under pleoptic treatment were examined The testing was performed before and after therapy Because the line acuity chart contains the rows 0 1–0.5 only the material contains those patients whose line acuity was not more than 0 33 at the end of therapy



Fig

Snellen and single E acuities before and after pleoptic treatment compared with line acuity given by the straight line See text

Results

The results are presented in Fig 2 The line acuity is given on the vertical axis and Snellen acuity and single E acuity on the horizontal axis on a geometric scale Each point represents the average visual acuity of 12-18 patients The figure beside the points denotes the superiority of Snellen acuity and single E acuity over line acuity

The results show that the difference between line acuity and Snellen acuity was significant only in the 0 1 and 0 05 groups in which Snellen acuity was clearly better These are examined in the Snellen chart with a single letter only Vision determined by isolated E symbols was always superior to line vision The difference was not linear however in that it was significantly greater at 0 1 and 0 05 The greatest difference was 5 8 fold The result concurs with an earlier finding that the separation difficulty grows when visual acuity diminishes (Stuart & Brian 1962) It was also observed that the separation difficulty increased during treatment This means that single E acuity improves faster and in many cases more than line acuity As already mentioned the Figure shows only the cases in which line acuity was 0 33 at the most at the termination of therapy

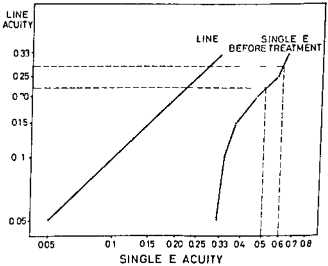


Fig 3

The difference between single E acuity and line acuity

Conclusion

Many factors e g the difference in illumination affect the differences between the results obtained with different charts However the most essential is the spacing between the letters and rows If the density of the chart is changed a different line acuity will be obtained The chart used by the author probably gives a fairy reliable idea of the development of line acuity during amblyopia treatment

In analysing the results there is a point that should be considered in vision screening studies for amblyopia (Fig 3) If the test used is one in which only one symbol is shown at a time which is fairly common the screening limit should be set sufficiently high since according to the above study the line acuity of a child seeing a 0 6 separate symbol is only about 0 25 Hence a part of the cases with amblyopia may pass the screening test However this presupposes that the separation difficulty of the four year old which is a common screening study age is of the same magnitude as that of the 7 to 10 year olds studied here

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Results

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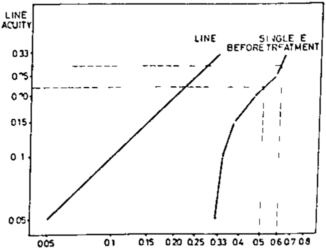


Fig 3

The difference between single E acuity and line acuity

A search of the literature revealed no reports on the use of lincomycin in the treatment of orbital cellulitis in children It was therefore thought appropriate to describe the following two cases

Case 1

The patient wa a 1? year old boy with multiple furunculosis Culture of pus gave growth of *Staph aureus* susceptible to penicillin tetracyclin and lincomycin but no antibiotic was given On the tenth day after onset the boy complained of headache and had a fever and swelling around the left eye He was admitted to hospital the following day Culture of nasal secretion and of fluid obtained from the eyelid yielded growth of *Staph aureus* only slightly susceptible to penicillin X ray examination revealed left sided pansinusitis The left eye was severely swollen red and tender and mildly protruded The veins of the fundus were somewhat dilated The papilla appeared normal Diagnosis orbital cellulitis The right eye appeared normal E.S R was 39 mm/hr

Treatment with penicillin was started at 6 7 mill I U./day parenterally The following day the treatment included in addition, oxitetracyclin 2 g/day perorally From the third day onward the boy was given penicillin perorally at 4 8 mill I U a day in addition to the tetracyclin. The treatment had no demonstrable effect on the eye or on the general condition After 4 days treatment penicillin and tetracyclin were replaced by lincomycin (Lincocin® Upjohn) intramuscularly 600 mg three times a day on the first two days and then 600 mg twice a day After two days treatment with lincomycin the patient was afebrile His general condition and his eye gradually improved

On the ninth day part of the eyelid fluctuated Incision allowed blood stained pus to escape Two days later lincomycin was given perorally and within the next five days the patient had completely recovered and was sent home The child had been given a total of 8 4 g lincomycin parenterally and 7 g lincomycin perorally

Case 2

The patient was a 10 year old girl with a painful swelling around the right eye mild fever and fatigue Five days after the onset right sided conjunctivitis with moderate periorbital edema was diagnosed E S R was 35 ml/hr Local sulphonamidtherapy was started

The patient did not improve and an ophthalmologic examination seven days later revealed a severe conjunctivitis and suspect incipient orbital cellulitis of the right side X ray examination of the nasal sinuses showed nothing remarkable X ray examination of the chest showed right sided small pneumoniae E S R was 57 mm/hr Treatment with penicillin at 1 8 mill I U a day perorally was started Despite penicillin treatment for one week the patient gradually became worse and severe orbital cellulitis was found The child was hospitalized

Examination on admission Right eye exophthalmus severe conjunctivitis chemosis and dense aqueous flare papilloedema spreading far out around the papilla Visual acuity 0 1 Left eye normal Penicillin was replaced by lincomycin parenterally 600 mg

From the Department of Ophthalmology and the Department of Pediatrics (Heads: Professor G. Österlind & Professor C.-C. Bergstrand) Malmö Allmänna Sjukhus, University of Lund, Sweden

EFFECT OF LINCOMYCIN ON ORBITAL CELLULITIS IN CHILDREN

BY

ANDERS SELLMAN and LENNART RIGHARD

Two cases of orbital cellulitis in children are described. Treatment with penicillin proved unsuccessful. Subsequent treatment with lincomycin parenterally produced rapid improvement and complete recovery from the infection.
The authors suggest that lincomycin should be considered in treatment of orbital cellulitis in cases where penicillin has no effect.

Key words: lincomycin – orbital cellulitis

Orbital cellulitis is fairly rare. Owing to its anatomical significance it is a potential threat to vision and even to life. Immediate and adequate treatment is therefore imperative. The condition may be secondary to some local periorbital infection, usually with staphylococci, streptococci or pneumococci, or to septicaemia. Orbital cellulitis usually is treated primarily with penicillin, which may, however, sometimes prove unsuccessful because of resistance of the bacteria to the antibiotic or insufficient local concentration of the latter.

Lincomycin is capable of destroying certain gram positive bacteria such as pneumococci, streptococci and staphylococci and has a good clinical effect on otherwise less readily accessible infectious processes in both soft and bony tissues (Geddes et al. 1964; Kaplan et al. 1965; Hnatko 1967; Holloway 1971 and others). Infections of the face have been treated successfully with lincomycin (Bentley & Pollock 1968; Gabka 1968; Dingman 1970).

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A search of the literature revealed no reports on the use of lincomycin in the treatment of orbital cellulitis in children It was therefore thought appropriate to describe the following two cases

Case 1

The patient was a 12 year old boy with multiple furunculosis Culture of pus gave growth of *Staph aureus* susceptible to penicillin tetracyclin and lincomycin, but no antibiotic was given. On the tenth day after onset the boy complained of headache and had a fever and swelling around the left eye He was admitted to hospital the following day Culture of nasal secretion and of fluid obtained from the eyelid yielded growth of *Staph aureus* only slightly susceptible to penicillin X ray examination revealed left sided pansinusitis The left eye was severely swollen red and tender and mildly protruded The veins of the fundus were somewhat dilated The papilla appeared normal Diagnosis orbital cellulitis The right eye appeared normal E.S R was 9 mm/hr

Treatment with penicillin was started at 6 7 mill I U./day parenterally The following day the treatment included in addition oxitetracyclin 2 g/day perorally From the third day onward the boy was given penicillin perorally at 4 8 mill I U a day in addition to the tetracyclin. The treatment had no demonstrable effect on the eye or on the general condition After 4 days treatment penicillin and tetracyclin were replaced by lincomycin (Lincocin® Upjohn) intramuscularly 600 mg three times a day on the first two days and then 600 mg twice a day After two days treatment with lincomycin the patient was afebrile His general condition and his eye gradually improved

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The patient did not improve and an ophthalmologic examination seven days later revealed a severe conjunctivitis and suspect incipient orbital cellulitis of the right side X ray examination of the nasal sinuses showed nothing remarkable X ray examination of the chest showed right sided small pneumoniae E S R was [illegible] mm/hr Treatment with penicillin at 1 8 mill I U a day perorally was started Despite penicillin treatment for one week the patient gradually became worse and severe orbital cellulitis was found The child was hospitalized.

Examination on admission Right eye exophthalmus severe conjunctivitis chemosis and dense aqueous flare papilloedema spreading far out around the papilla Visual acuity 0 1 Left eye normal Penicillin was replaced by lincomycin parenterally 600 mg

twice a day and tetracyclin 1 g/day perorally. After five days treatment improvement was noted. The inflammation was less severe, the papilloedema was decreasing and visual acuity was 0.5. Then lincomycin was given perorally [illegible]50 mg/day. The dose of tetracyclin was maintained unchanged. Four days later the patient was worse. Visual acuity fell to 0.1. In the fundus was seen an increasingly choked disc with wide tortuous veins and small haemorrhages. The peripapillary oedema extended into the area of the macula. Intraocular examination revealed an inward bulge af the entire posterior part of the pole. An abscess in the orbit behind the eye was suspected. The condition was regarded as critical. Parenteral lincomycin therapy at 1.2 g/day was started again. After five days a distinct improvement was found, the proptosis was less marked and visual acuity was 0.4. Since tetracyclin did not appear to have any effect it was replaced by cloxacillin perorally 4 g/day. Lincomycin *i.m.* 1.2 g/day was continued for 24 days followed by 0.6 g/day for the following 5 days. Totally 59 g lincomycin was given parenterally and 4.5 g perorally. During the treatment the patient steadily improved and made a complete recovery. The visual acuity was 1.0 on both eyes. No bacteriological diagnosis was obtained, but the course of the condition strongly suggested staphylococcal infection.

Discussion

Antibiotic treatment of orbital cellulitis is sometimes unsuccessful because of the resistance of the bacteria to the antibiotics used or to insufficient concentration of the antibiotic in the tissue affected. In *case 1* the patient had furunculosis caused by penicillin susceptible staphylococci but culture of nasal secretion six days later yielded staphylococci that were only slightly susceptible to penicillin. Penicillin had no demonstrable clinical effect, probably because of insufficient concentration in the affected tissues and/or because of the poor susceptibility of the bacteria. Therefore penicillin was replaced by lincomycin, which reaches even less accessible foci in high concentrations and is effective against gram positive bacteria. Besides, Kaplan et al. (1965), Vacek et al. (1969) have shown that the level of lincomycin in the plasma is considerably higher when the substance is given parenterally than when it is given perorally. In *case 2* lincomycin was first given parenterally but afterwards perorally, which resulted in clinical deterioration. Lincomycin should therefore be given parenterally in a large dose and for a sufficient period of time.

The only side effect of lincomycin observed was a slight tenderness over the site of injection. Given perorally lincomycin may have intestinal side effects ranging from mild diarrhoea to occasionally, though very rarely, fulminant colitis (Pittman & Pittman 1970, 1971, Benner & Tellman 1970, Ecker et al. 1970). Mild side effects on the skin (rashes and urticaria) have also been observed in some cases (Herrell 1968).

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EFFECTS OF REPEATED TONOMETRY: GENUINE AND SHAM MEASUREMENTS

BY

K. WILKE

Repeated applanation tonometry every minute in normal subjects gave a direct pressure reduction of about 3 mmHg in five minutes and a lower consensual pressure reduction. Sham measurements had no corresponding effect, nor was the initial IOP reduced after sitting at the tonometer for five minutes before tonometry. The spacing of the measurements and the length of time the applanation body was left on the cornea influenced the decrease curve.

Key words: applanation tonometry – sham measurements – consensual pressure reduction.

Since Stocker (1958) observed a pressure reduction following repeated tonometry, this phenomenon has been studied by several authors (Moses 1961, Bechrakis 1966, and others). Several aspects of their results have been confirmed in experiments by the present author. The direct pressure reduction amounts to 3–4 mmHg in 5 minutes and follows a curve which no doubt is well described by an exponential function. There is, however, an important point on which the findings made in our laboratory are not in accordance with those of Moses and Bechrakis. These authors claim that sham measurements are as efficient as true measurements in reducing the pressure. This is difficult to reconcile with ob-

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servations made with the vibration tonometer (Krakau & Wilke 1971) where the pressure reduction was found to be correlated to the weight of the tonometer on the cornea

If sham measurements were efficient in producing the pressure decrease one could hardly expect this decrease to depend on the mode of measurement either It was felt that the possible role of sham measurement had to be determined before the mechanism of the phenomenon could be approached

The aim of the present paper is then to repeat the sham experiments and also to study the effect of some variations in the applanation procedure

Methods

All measurements of the IOP were made by means of Goldmann s applanation tonometer Local anaesthesia with Novesin 0 4 %® was used The instillation is marked by an arrow in the Figures Fluorescein from paper strips was introduced once or several times during a series The measurements *were made* quickly as a rule the time for the procedure was 5–10 seconds unless otherwise stated Only in one type of series of measurements did the applanation body of the tonometer rest for 30 seconds on the cornea on each occasion In these series the IOP was read at the beginning and the end of *each measurement*

Material and Methods

Four series of measurements (A B C D) intended to elucidate the effect of sham measurements were made on six healthy women aged 17–52 and every series was repeated three times in each subject

In series A the first measurement was made on both eyes as the patient was placed at the tonometer and the second measurement was taken five minutes later

In series B the first *measurement* was made as in series A and then the IOP was measured once a *minute* for five minutes on the right eye and finally the IOP was measured again on the left eye

In series C the patient was seated at the tonometer for five minutes after having local anaesthesia before the measurements were performed exactly as in series B

Series D started with a series of sham measurements where the plexiglass body of the tonometer was brought close to the cornea but not allowed to touch it Otherwise the procedure was the same as in *series* B A series of true

measurements as in series B followed the sham measurements immediately The patient was not informed whether sham measurements or true measurements were being made The four series A B C D were taken in random order and only one series was made every day

In order to study *the restitution of the pressure* the IOP was measured on both eyes five ten or fifteen minutes after the last measurement in series B C or D

A series of type B was also made on 53 other patients with normal eyes or with glaucoma and with different IOP to find out whether the pressure decrease was correlated to the IOP

Series of type B made on three of the normal female subjects were compared with two other series which closely resembled series B but in the first series there was an interval of two minutes between every measurement and in the second series the duration of the measuring procedure was 30 seconds These two series as well as series B were repeated five times each on all subjects

Results

Fig 1 shows the mean values of the measurements in series A B C and D and Table I summarizes the pressure reductions with reference to their statistical significance

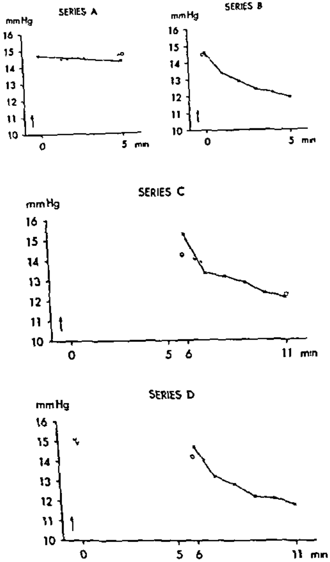
In *series A* there was no significant difference in IOP between the first *measurement and the second 5 minutes later On the right eye there* was a pressure decrease of 0 4 mmHg and on the left eye there was a pressure increase of 0 1 mmHg

In *series B* there was a significant pressure decrease of 2 6 mmHg after repeated measurements on the right eye and a consensual pressure decrease in the left eye of 1 8 mmHg

The results of *series C* were similar to those of series B The pressure fell 3 ? mmHg on the right eye and the consensual pressure 2 0 mmHg on the left eye The level of the initial pressure was not significantly *different from that of* series A and B

In *series D* the pressure after the sham measurements was not significantly different from the initial pressure in the other three series and during the true measurements there was a pressure decrease of 2 9 mmHg on the right eye and a *consensual pressure decrease of 1 5 mmHg on the left eye*

Since no significant differences in the pressure effect between the series B C and D were observed and since these series were mixed in a random way during the investigation it seems justified to compare the pressure effects at the



Fi 1

Mean values of the measurements in series A B C, and D
ght eye ⊂ = left eye ◡ sham measurements ↑ = instillation of Novesin®

beginning and at the end of the series The whole group of series covers a period of about one month and there might possibly be some change of the response with time say a reduction due to some kind of adaptation to the procedure

Table I

		Mean (mmHg)	t	P
I	ΔP (A)	0.4	1.75	>0.10
	ΔP (B)	2.6	13.0	<0.001
	ΔP (C)	3.2	15.1	<0.001
	ΔP (D)	2.9	18.0	<0.001
	ΔP (B) – ΔP (C)	0.6	2.84	0.05–0.0[illegible]
	ΔP (B) – ΔP (D)	0.3	0.75	>0.50
II	P_0 (A) – P_0 (B)	0.1	0.32	>0.[illegible]0
	P_0(A) – P_0 (C)	0.6	0.59	>0.60
	P_0(A) – P_0 (D)	0.0	0.04	>0.95

P_0(A) etc = initial IOP (mean) right eye series A etc
ΔP(A) etc = pressure decrease (mean) right eye series A etc
The calculations are based on the mean values from the six individuals. In group I the hypothesis $\Delta P = 0$ was tested. In group II pair differences were tested. Student's t test has been applied.

The mean pressure decrease of the first and last three series on each subject irrespective of which kind of series was made was therefore calculated. These were 2.7 and 3.1 mmHg respectively. There was no significant difference between measurements made at the beginning and at the end of the investigation. This is also illustrated in Fig. 2, which shows the results on two subjects in which identical measurements of type B were repeated daily for six days.

In Fig. 3 the pressure reduction (ΔP) in the individual 54 series from the 6 subjects in series B, C and D was plotted against the initial IOP (P_0) (black dots). The ΔP from the 33 other patients with different P_0 on whom we made a series B is shown in the same figure.

The regression line for one series B from all 39 subjects was calculated and found to be $y = 2.36 + 0.0525x$, $r = 0.29$ (Fig. 3), where P_0 is the independent and ΔP the random variable.

When IOP was measured 5, 10 or 15 minutes after the last measurement in series B, C or D, there was a restoration of the pressure to 67 %, 69 % or 75 % of the pressure reduction.

Fig. 4 shows the mean values from the 3 different kinds of measurement arranged as the B series taken on 8 subjects. In the ordinary series B (marked with crosses) (applanation surface on the cornea for 5–10 sec at each pressure

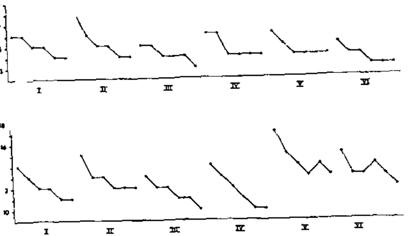


Fig 9

B series measurements from right eye in two subjects on six consecutive days

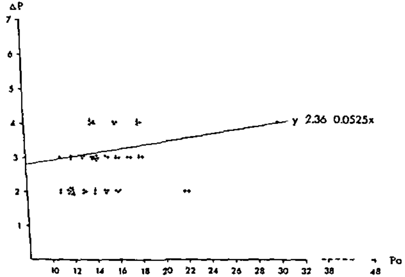


Fig 3

Pressure reduction (ordinate axis) in relation to initial IOP (abscissa axis)

- measurement in series B C, and D on six subjects

I the first B series in these six normal subjects

measurements on 33 patients with different IOP

The regression line is calculated from the group of measurements marked I and +

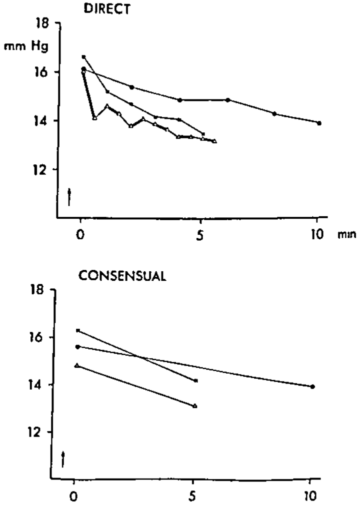


Fig 4

Mean values of direct and consensual pressure reduction in three different series in three subjects

● – measurements taken every second minute

× = measurements taken every minute

△ = measurement where the measuring body was left on the cornea for 30 seconds (thick line) One value was taken at the beginning and one at the end of this period

recording) there was a direct pressure reduction of 3 1 mmHg and a consensual pressure decrease of 2 1 mmHg In the series with 2 min between each measurement there was a direct pressure reduction of 2 2 mmHg and a consensual pressure reduction of 1 7 mmHg after 10 min When the plexiglass body rested for 30 seconds on the cornea on each occasion (marked with triangles) there

was a pressure reduction of 2 8 mmHg following repeated measurements and the pressure decrease was most evident during the first measurement The consensual pressure fall was 1 7 mmHg

Discussion

The subjects in the experiments with repeated tonometry were well acquainted with the applanation procedure Some of the subjects have been used for long periods and hundreds of series varied in some respects have been made on the same individual No tendency towards reduction of the responses after a great number of series has been found The two series in Fig 2 are examples of some identically repeated measurements performed daily on such well trained persons It is not probable that the pressure decrease is the result of some transitory tension elicited at a measurement It will not be denied how ever that when encountering tonometry for the first time the subject may feel strained and therefore may exhibit unusual or irregular responses to the tono meter but such initial effects are excluded in the present series

Nothing supports the idea that sham measurements are efficient in provoking a pressure reduction as is evident from series D The results in series A B C and D indicate clearly that only genuine repeated measurements elicit a pressure reduction

The pressure reduction seems to be of a similar magnitude in all series with repeated measurements though with a slightly higher depression at higher IOP (Fig 3) If the decrease were to be attributed to a constant volume of aqueous being withdrawn from the eye a considerably higher pressure effect would be expected at higher than at lower pressure levels

The procedure at measurement can be varied and the series in Fig 4 show that this influences the results entirely in accordance with our previous results with loading of the measuring body of the vibration tonometer

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EFFECT OF VISIBLE LIGHT ON PHOSPHOLIPID AND CHOLINESTERASE OF THE CHICKEN RETINA

BY

S R BAWA and RAKESH C YASHROY

Chickens were adapted to dark and light for 30 days and their retinas were studied in comparison to the chickens kept in normal environments Total phospholipid content and cholinesterase activity were determined biochemically in the retinas of each group of animals An increase of approximately 7 % was observed in the phospholipid content of the dark adapted retinas whereas the light adapted retinas showed no significant change in comparison with the normal counterparts Retinal cholinesterase activity decreases by about 64 % on dark adaptation and increases by about 14 % on light adaptation

Key words retina – chicken – phospholipid – cholinesterase – light

The study of physiological changes caused by dark and light adaptation of the retina has been of great interest recently because such studies give direct understanding of the functioning of this organ Real function of retina starts only when light reaches it It is therefore of fundamental importance to investigate what happens to the retina if it is maintained in the absence or presence of light

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Rasch et al (1959) recorded decreased RNA and protein contents of the cat retina subsequent to monocular light deprivation Alkaline phosphatase activity increases on dark adaptation and decreases on light adaptation in the retina of *Calotes Versicolor* (Tewari & Tyagi 1968) and chicken (Bawa & YashRoy 1972) Maraini Carta & Franguelli (1969) showed decreased acetylcholine esterase activity on monocular light deprivation of rat retina Studies on the variation of glycogen and nucleic acid contents of dark and light adapted chicken retinas have been reported previously (Bawa & YashRoy 197[illegible]) The present paper deals with further investigations on the variation of phospholipid content and cholinesterase activity in chicken retina subsequent to 30 days of dark and light adaptation

Materials and Methods

Thirty 2½ month old broiler chickens were divided into 3 equal groups One group was kept in dark for 30 days while the second was exposed to a 100 watt electric bulb fixed at the center of the cage measuring 3 × 3 ft and provided with a fan The third group of chickens was kept in a normal environment and served as a control The animals were beheaded without anaesthesia and the retinae were removed after enucleation of the eyes

Total phospholipid content of the retinal samples was determined by measuring phosphorous (Fiske & Subbarow 1925) using the method cited by Varley

Table I

Effect of dark and light adaptation (30 days) on the phospholipid content and the cholinesterase activity of the chicken retina

Adaptation (30 days)	Phospholipid mg per g retina ± SD	Cholinesterase activity mg acetylcholine hydrolysed per g retina ± SD
Dark	11 00 ± 0 81	6 54 ± 0 98
Light	9 10 ± 1 01	21 10 ± 1 40
Control	9 10 ± 0 94	18 45 ± 1 70

(1967) Cholinesterase activity was estimated by the method cited by Natelson (1961) employing acetylcholine chloride as the substrate by incubating tissue homogenate with the substrate for 1 h at 37 C

Results

The Table shows that phospholipid increases by approximately 22 % in the retinas adapted to dark for 30 days in comparison to normal retinas Cholinesterase activity decreases by about 64 % on dark adaptation and increases by nearly 14 % on light adaptation of the chicken retina

Discussion

Phospholipid content of the dark adapted retina is approximately 22 % higher than that of light adapted and normal retinas Day & Fidge (1965) have shown in macrophages that glucose is converted to glycerol which in turn reacts with fatty acids to form triglycerides and finally the phospholipid Such a mechanism has not yet been reported in the retina however it is suspected that it may be one of the modes of synthesis of phospholipid from glucose on prolonged dark adaptation In our previous report (Bawa & YashRoy 1972) we have contended that during prolonged absence of light the energy requirement of the retina is less and a considerable part of the glucose supplied to the retina is converted to glycogen (glycogenesis) And it is plausible that a part of it (glucose) may be converted to phospholipid as is suggested by the findings of Day & Fidge (1965)

The process of lipogenesis may be assisted by alkaline phosphatase *since* Lindeman (1949) while studying the development of the chicken retina observed that alkaline phosphatase activity appears at the time when *phospholi*pid rich membranes of photoreceptor outer segments are formed This view gets added support from our observations that there exists a *parallel increase* in the phospholipid content and the alkaline phosphatase activity *of chicken* retina on gamma irradiation (Bawa & YashRoy 1971a) and dark and light adaptation (Bawa & YashRoy 1971b)

Dark adaptation is the process during which the retina not only builds up its light degenerated photopigments but also replenishes itself with the nutrients depleted during light exposure *Regeneration* of photopigments is completed in

a few minutes of dark adaptation whereas the synthesis of such nutrients as glycogen and lipids continues for long periods Phospholipid forms an essential constituent of biological membranes and when it occurs in combination with proteins it is called proteolipid Combination of lipids with the photopigments is rather clearly shown by the observation of Adams ([illegible]) that chloroform methanol (2 1) removes a significantly greater quantity of lipid from bleached bovine retinal rods than from their dark adapted counterparts Thus during dark adaptation when the photopigments are rapidly synthesizing the increase in phospholipid content (associated with these pigments) can clearly be visualized It is therefore expected that the lamellar system (disks) of photoreceptor outer segments which are rich in phospholipid should be very well formed subsequent to dark adaptation Sosula & Glow (1971) reported an increase in the number of synapses in the inner plexiform layer of light deprived rat retinae Like all membranes synaptic membranes are also rich in phospholipid and thus this information is in line with our observation

Cholinesterase activity is markedly reduced (64 % approximately) on dark adaptation but it slightly increases (14 % approximately) after light adaptation of the chicken retina Liberman (1962) reports that in the retina of total cholinesterase (acetylcholinesterase plus pseudo cholinesterase) [illegible] % of the activity is due to acetylcholinesterase The changes recorded by us are consistent with the observations of Marani Carta & Franguelli (1969) who reported significant decrease in acetylcholinesterase activity of the retina and lateral geniculate nucleus of the eye monocularly deprived of light in new born rats Acetylcholinesterase hydrolyses the neurotransmitter acetylcholine and this enzyme is responsible for the synaptic transmission of the nerve impulse As evidenced by the electrophysiological observations electrical activity of the retina shoots up on stimulation by light and hence cholinesterase activity must increase accordingly to cope with the increased synaptic transmission of impulses

By injecting monocularly light exposed rats with the irreversible inhibitor of acetylcholinesterase di isopropyl fluorophosphate (DFP) Glow & Rose (1964) discovered that *de novo* synthesis of acetylcholinesterase occurred considerably faster in the light stimulated retinas in contrast to their light deprived counterparts The fall of cholinesterase activity observed by us can safely be interpreted as due to a decrease in the synaptic activity of the retina during dark adaptation Nichols & Koelle (1968) demonstrated the presence of acetylcholinesterase activity in the synaptic layers (inner and outer plexiform layers) and amacrine cells in pigeon ground squirrel rabbit rat and cat retinas They concluded that amacrine cells are the major source of acetylcholinesterase for the inner plexiform layer and at this site the enzyme is con

cerned with the synaptic transmission because the bands showing enzyme activity in this layer represent anatomically the stratified terminal arboriza tions (synaptic endings) of the amacrine cells

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BINOCULAR VISION IN MONOCULAR APHAKIA CORRECTIBLE BY CONTACT LENSES

S VANNAS A VANNAS R BLOMSTER and J VALTONEN

The material consisted of 32 patients with monocular aphakia 22 of which were of traumatic and 10 of a non traumatic origin Early cataract extraction and the fitting of contact lenses as well as a symmetrical central positioning were regarded as favourable for binocular vision The small types of lenticular lenses with modified contour construction (A Linssi) were used the most but especially for children Griffin's Bionite soft lenses were necessary
Orthoptic treatment was helpful in achieving binocular vision Manifest strabismus occurred when the delay in the fitting of contact lenses was more than 6 months Surgery and orthoptic respectively pleoptic treatment may be of benefit even in these cases
The delay in cataract extraction and the fitting of contact lenses was the most damaging for children Since relapses occur more easily in children than in adults they must remain under close observation.

Key words monocular aphakia – delay in the fitting of contact lenses – contact lens of small lenticular type – scleral lens soft lens – binocular vision – orthoptic treatment

Monocular cataract leads to loss of binocular vision As trauma seems the most common cause monocular aphakia causes disablement especially in men of all ages Cataract extraction often is postponed for a considerable time During

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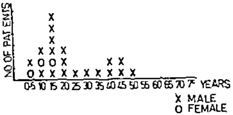


Fig 2

Age distribution of the patients at the time of the trauma

not included Different types and degrees of corneal scarring even in the optic area were present Pupillary deformation as well as secondary cataract at the pupillary border occurred in some cases Three patients had secondary glau coma

Methods

For aphakic contact lenses the small types of lenticular lenses and minus car rier lenticular lenses with modified contour construction (A Linssi) were mostly used in two cases however scleral lenses were necessary Keratometer readings and the fluorescein pattern were preferred in the fitting procedure but even moulding was necessary in some cases To avoid artificial hyper phoria and distortion in the spatial stereoscopic relationship symmetric center ing was regarded as essential and close laboratory co operation was invaluable

In seven very sensitive eyes Griffin s Bionite soft lenses proved the method of choice They gave as good a visual acuity as lenticular lenses did and no adaptation period was necessary Soft contact lenses seemed an ideal solution especially for children as suggested earlier (Kaufman & Uotila 1970 Dreifus 1971) When astigmatism exceeded 2 D an additional correction generally was necessary It was combined with bifocals used as a near correction for all pa tients Hexol (Trager et al 1972) was used for the sterilisation of soft lenses There were no complications

Binocular vision was examined immediately after the fitting of contact lenses and again after the surgical correction for manifest squinting where necessary The routine orthoptic examination was completed with an aniseikonia test using Ames s space eikonometer (1945)

Orthoptic treatment was offered in order to develop or to increase conver

the 1940 s attention was paid to the optical correction of monocular aphakia by means of contact lenses (Gyorffy 1950) In Ruben s (1962) and Mills & Terry Lewis s (1971) series however half of the patients who were corrected with scleral contact lenses gave up wearing them Further according to Lyle (1953) and Ridley (1953) about 50 per cent did not achieve any useful binocular vision

The purpose of this report is to deal with binocularity problems in monocular aphakia corrected by means of contact lenses The investigation was carried out as teamwork by the contact lens laboratory and the orthoptic department In this way a survey of the factors influencing the final binocularity such as the degree of squint related to the delay between the cataract operation and the fitting of the contact lens was worked out

Material

The material was selected between 1970 and 1971 and consisted of monocular cataract patients from the files of our department fresh traumatic cataracts and patients with monocular aphakia receiving treatment for complications such as squint The material consists of 32 patients (Fig 1) 23 men and 9 women The age distribution was 4–72 years (mean age 35 9 years) Twenty two patients had traumatic and 10 non traumatic cataract The right eye was affected in 17 and the left in 15 cases The time of observation after fitting of the contact lens averaged 14 months

The majority belong to the traumatic cataract group (Fig 2) and the age distribution at the time of injury was 1–46 years the mean age being 21 years The interval from the accident to cataract extraction was up to 28 years Corrected visual acuity through the pinhole varied from 0 7 to 1 3 amblyopic eyes

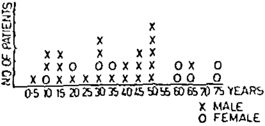


Fig 1
Age and sex incidence in 32 cases

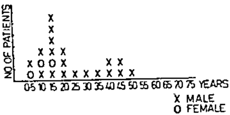


Fig 9
Age distribution of the patients at the time of the trauma

not included Different types and degrees of corneal scarring even in the optic area were present Pupillary deformation as well as secondary cataract at the pupillary border occurred in some cases Three patients had secondary glaucoma

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gence amplitude of fusion and acuity of stereoscopic vision In three children even pleoptics were needed The length of the series required varied rather considerably

Results

Corneal contact lenses were as a rule well tolerated by the patients In cases of irritation when the patient was unable to wear the lenses for at least 6–8 hours a day the lenses were adjusted and new lenses were occasionally made – a procedure which often was of help Dusty work made the continuous wear of contact lenses impossible in one particular case Two patients gave up be cause of diplopia

Griffin s soft lenses were tolerated for the whole day without irritation but upon removal difficulties occasionally occurred and from time to time they ruptured and had to be replaced

Visual acuity

Corrected visual acuity of the aphakic eye in general was normal despite corneal scarring In 29 eyes visual acuity was $\geqq 0\ 8$ Three children had developed amblyopia The youngest patient a 1 year old boy in whom a scleral contact lens was fitted one year later had developed amblyopia and esotropia Occlusion therapy and operative correction of the strabismus were necessary He wears contact lenses all the time At the beginning he had all day occlusion then after surgery for strabismus 4 hours a day occlusion At the age of 4 years vision is now 0 25 and the eye has started to squint again Pleoptics are started at the age of 5 years A boy of 5 years became amblyopic already after 4 months but he and an 8 year old girl did well with pleoptics

In older patients delay in cataract extraction or in the fitting of contact lenses did not influence visual acuity The longest interval was 28 years A perforating injury had occurred at the age of 12 and normal visual acuity was achieved when the patient was 40 Visual acuity was also normal in a woman aged 59 after a 16 year interval

The final visual acuity with contact lenses was in general the same as the initial visual acuity except in cases with amblyopia However in two patients the final visual acuity was less due to macular degeneration in one case and unoperated retinal detachment in another Three children developed myopia of the fellow eye later and one of them developed at the same time exotropia and amblyopia of the aphakic eye

Table I

Type of squint with a contact lens before (A) and after (B) surgery and/or orthoptic training

	A	B
Heterophoria	17	25
Heterophoria near / Heterotropia distance	4	0
Heterotropia	11	3+2
Total	32	32

Vision lost due to 1) retinal detachment
2) macular degeneration

Binocularity

Heterophorias were found in 17 patients after the fitting of contact lenses (Table I) Heterotropia was diagnosed in 11 patients The rest had a tropia for distance and a phoria for near vision

Time factor It seemed of interest to correlate the time lapse from the trauma to the contact lens fitting with the frequency that surgery was needed to correct a manifest squint Traumatic cataract was divided into three groups according to delay in the fitting of contact lenses (Fig 3) 7 patients with a delay of less than 6 months 8 patients with less than 24 months and 7 patients with more than 24 months The non traumatic aphakic series was considered a

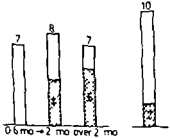


Fig 3

The delay in the fitting of contact lens and the frequency of strabismus surgery required in traumatic cases related to 10 non traumatic cases

Table II
Worth's Four Dot Test with a contact lens and a bifocal before (A) and after (B) the series of orthoptic training

	A		B	
	Distance	Near	Distance	Near
Five dots	13	9	4	3
Four dots	16	20	22	24
Suppression or unknown	3	3	4+2*	3+2*
Total	32	32	32	32

* Vision lost due to 1) retinal detachment
2) macular degeneration

group of its own In the series with the time interval of less than 6 months none required surgery for squint of the group of less than 24 months half required surgery for squint and in the series of over 24 months 71 per cent were operated on The youngest patients had had the greatest risk of squint Two of the non traumatic group had manifest strabismus and required surgery

After surgery for squint orthoptic treatment was administered as well as for mere heterophoria (Table I) At first single vision was obtained for near vision However in the heterophoria group the orthoptic treatment was considerably shorter or sometimes unnecessary

Diplopia (Table II) disappeared in 9 cases out of 13 but in 4 cases it is still present Two of these have given up the use of contact lenses and in two orthoptic treatment is continued

Fusional amplitude was rather limited or lacking in half of the patients but during the treatment it increased in 15 cases (Table III) For correction of vertical deviations prisms have been used successfully except in two cases In them ex cyclo apparently made fusion amplitude difficult to attain In two further cases macular degeneration or retinal detachment had developed during the time of observation and fusion amplitude was lost as well as binocular vision

Stereoscopic vision improved in 10 cases (Table IV) Interestingly enough stereoscopic vision evolved in 6 cases with diplopia and tropia for distance but phoria for near vision was present immediately after the fitting of contact lenses or after surgery

Table III

Fusion amplitude with a contact lens before (A) and after (B) the series of orthoptic training

	A	B
Adduction $< 10°$	15	2
< 20	9	8
≥ 20	3	15
Suppression or unknown	5	5+2
Total	32	32

* Vision lost due to 1) retinal detachment
2) macular degeneration

Discussion

Good visual acuity for distance and near vision is necessary for binocularity The high quality of the contact lenses and the comfortable adaptation and tolerance are important as is the prescription of bifocals for near vision In our material the wearing time was usually the whole day and at the least six hours a day The fitting and adjusting of corneal contact lenses for traumatised eyes has caused many problems and would not be successful without close co operation with a contact lens laboratory

Our results further showed that the time interval during which binocularity had been interrupted correlated with the frequency of the manifest squint Half

Table IV

Stereoscopic vision with a contact lens as graded by synoptophore Clement Clarke before (A) and after (B) series of orthoptic training

	A	B
Good stereopsis	14	11
Moderate stereopsis	4	4
Slight stereopsis	3	
No stereopsis		9
Unknown	4	4
Total	3	

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of the patients indeed had obvious binocular difficulties A manifest pre operative deviation especially if severe enough to warrant strabismus surgery is considered to carry a poor prognosis (Mills & Terry Lewis 1971) According to Fonda (1971) certain ocular motility problems may contraindicate the fitting of contact lenses Our results clearly indicated that strabismus surgery *and orthoptics with contact lenses may lead to firm binocular vision but much* is due to the patient s motivation Further in these cases orthoptic treatment may be rather laborious

The delay in cataract extraction and the fitting of contact lenses was most damaging for children due to the risk of amblyopia and suppression of the af fected eye On the other hand even good results in children required continued control during adolescence Development of myopia for example could lead to manifest squint and jeopardise the results

If the fitting of the contact lens is performed in due time when the patient still has some binocular vision left the orthoptic treatment seems to improve fusion and stereoscopic vision remarkably this probably has great importance *for fixing the binocular results permanently*

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are generally lanugolike shorter thinner and lighter than normal cilia The patients usually complain of photophobia tearing blepharospasm and a feeling of sand in the eyes In most cases some of the aberrant lashes rub against the bulbar conjunctiva and cornea producing conjunctivitis keratitis and corneal ulcers Corneal opacities are rare however The aberrant cilia vary widely in the number appearance and direction of their shafts Some patients have only a few additional lashes in one or two lids in areas in which the orifices of the meibomian glands usually open Others have an almost complete accessory row of lashes in all four lids Distichiasis which is a congenital condition must be differentiated from acquired abnormal condition known as trichiasis a word which indicates malposition and maldirection of the lashes

The literature on congenital distichiasis is quite scanty The first theory to explain the occurrence of distichiasis was advanced by Kuhnt (1899) who considered that distichiasis is a heterotopic abnormality in which the meibomian glands are replaced by true cilia with characteristic adnexa In Begle s case (1913) meibomian glands were replaced bv hyperplastic sebaceous glands discharging into the follicles of well developed accessory cilia He suggested that distichiasis may be an atavistic phenomenon in which glands of a highly modified type fail to develop and are replaced by similar structures which are more primitive phylogenetically In von Szily s case (19_3) the posterior cilia emerged from the orifices of the rudimentary meibomian glands The tarsus was of normal firmness length and width In his opinion congenital distichiasis is merely a return in parts to a phylogenetically earlier form Blatt (19?4) also accepted the atavistic theory of its origin

The possible hereditary factor in distichiasis was discussed in many reports Erdmann (1904) first reported distichiasis in three generations Blatt s (1924) contribution was particularly important from the standpoint of the hereditary factor His five cases indicated autosomal dominant inheritance showing the affection in three generations in both sexes Pico (19?9) reported the mode of inheritance of distichiasis to be of an autosomal dominant type He reported 10 cases in one family eight of which also showed congenital ectropion and gave a wide review of the previous literature in his article A more detailed account of these earlier reports can be obtained from Pico s article and also from a paper by Fox (1962) who reported a total of ?8 cases of distichiasis found in the literature up to that date He also described a successful surgical procedure for the correction of distichiasis Scheie & Albert (1966) used the operating microscope for the removal of aberrant lashes with electrolysis

This paper reports eleven cases of congenital distichiasis and an investigation of the mode of inheritance

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CONGENITAL DISTICHIASIS

A Report of Eleven Cases and an Investigation of the Mode of Inheritance

BY

EILA MUSTONEN

Three separate families were examined in three generations after one case of distichiasis had by chance been found in every family. No history of consanguinity was found in these families. In the first family 48 members were examined, 45 of them personally by the writer. Nine subjects, most of them myopic, were found to have distichiasis. In the second family 39 members were personally examined and no other case of distichiasis was found. The one patient was myopic. The third family with 7 examined members had also only one case of distichiasis. This patient was hyperopic. Histopathology was studied after two patients from the first family had been operated because of irritation of the eyes by aberrant lashes. The mode of inheritance seemed to be autosomal dominant with quite high penetrance. Of the total 11 cases 8 were myopic.

Key words: distichiasis – meibomian glands – myopia.

Distichiasis, a term derived from the Greek words (di = two, stichos = row) indicates the presence of an aberrant posterior row of eyelashes which emerge from the sites of the normal openings of the meibomian glands. The lashes

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Table I

The cases of d stichiasis The results of retinoscopy and keratometry The depth of the anterior chamber The axial length of the eyeball

Case No		Refraction by retinoscopy in diopters	Corneal refraction by Javal Schiotz keratometer in diopters		Depth of anterior chamber (mm)	Axial length of eyeball (mm)
1	R	−9 0 cyl −2 5 × 0°	41 5 × 0	43 5 × 90°	2 5	26 [illegible]
	L	− 5 cyl −2 5 × 0°	41 5 × 0°	42 5 × 90	2 5	25 4
2	R	−16	43 5 × 0	45 5 × 90	2 5	23 0
	L	−20	43 5 × 0°	45 0 × 90	2.5	29 0
3	R	+ 0 25 cyl + 0 5 × 80°	44 0 × 1 0	44 0 × 50	2 5	not
	L	+ 0 5 cyl + 0 5 × 100	43 5 × 10	44 0 × 100°	2 5	measured
4	R	−0 cyl −0 25 × 0	42 0 × 15°	43 0 × 105	2 8	24 0
	L	−0 5 cyl −0 25 × 0	42 0 × 5	42 5 × 35°	2 8	24 0
5	R	−1 5 cyl −1 0 × 100°	43 0 × 0°	43 0 × 90	3 2	not
	L	−1 5 cyl −1 0 × 70	43 0 × 0°	43 0 × 90	3 2	measured
6	R	−1 5 cyl −0 5 × 0°	42 0 × 0°	43 0 × 90	3.2	not
	L	−1 25	42 0 × 0	4 0 × 90	3 2	measured
7	R	+ 0 5 cyl −2 5 × 175	43 0 × 160	44 5 × 0	2 4	2[illegible] 8
	L	−1 5 cyl −0 5 × 80	44 0 × 0	43 5 × 90	4	22 9
8	R	−0 25 cyl −0 75 × 90	not measured		not measured	not measured
	L	−0 5				
9	R	+ 0 5	43 0 × 160	4 0 × 70	not measured	not measured
	L	+ 0 5	43 5 × 15°	42 5 × 105°		
10	R	−0 5 cyl −0 25 × 0	40 5 × 0	41 5 × 90	3 2	25 0
	L	−0 5 cyl −0 25 × 0°	41 0 × 0°	4 0 × 90	3 2	25 0
11	R	+ 0 75	44 0 × 0	45 0 × 90°	3 0	21 5
	L	+ 0 75	43 5 × 0	44 5 × 90°	3 0	21 5

not yet satisfa tory The histopathological examination revealed both normal and atrophic meibomian glands with lashes rising from them

Of this pat ent s mother s family 18 members in three generations were examined and n cases of d stich a is were found The pedigree (Fig 3) presents the father s family of which 9 members in th ee generations were examined and 8 additional cases f d stich as s were found Ne ther the father nor the mother of the girl h d di tichiasis but the father was myopic Two paternal uncles had myopia but not distich as s The paternal grandmother had marked myopia and also d stichiasis All the cases of distichiasis are presented in detail

Case 2 I H

The 69 year old paternal grandmother of Case 1 (Fig 3 II 1) had been markedly myopic the wh le f her l fe The v sual acu ty of both her eyes was reduced because

Material and Methods

Three entirely separate families comprising 94 examined members were investigated with biomicroscopy ophthalmoscopy and retinoscopy Most of the eleven patients who had distichiasis were examined by Javal Schiotz keratometer for corneal measuring the axial length of the eyes was measured by ultrasound technic and the depth of the anterior chamber was estimated Two of the patients were operated and the histopathological examination was performed from the excised flaps of lid margin with aberrant lashes

Results

All the cases of distichiasis are presented in detail Table I shows the findings not given in the text Visual acuity was normal with a correction except in one patient who had myopic fundus changes The aberrant lashes situated in the normal location of the meibomian orifices and the other parts of lid margins were normal

FAMILY 1

Case 1 E H

An 11 year old girl (generation IV number 7 the propositus in the pedigree Fig 3) was admitted to our outpatient eye clinic in May 1971 from the psychiatric department of the pediatric clinic where she was being investigated because of mental retardation enuresis and encopresis She had also had recurrent pyelonephritis Since early childhood she had been myopic She complained of tearing photophobia and a feeling of sand particularly in her right eye The slit lamp examination revealed in both eyes small epithelial erosions of cornea mostly in the lower part No corneal opacities were found In both eyes the lower and upper eyelashes were in a normal position at the anterior border of the lid margin but there was an accessory row of lashes in all four lids close to the inner border of the lid margin in the normal location of the meibomian orifices The lower lids both showed 19 additional lashes the right upper lid had 21 and the left upper lid 24 additional lashes (Figs 1 and 2) The aberrant lashes were turned inwards and rubbed against the cornea in both eyes No other anomalies besides this accessory row of lashes in all four lid were found

It was decided to perform plastic lid surgery and first the right upper and lower lid were operated with Fox technic (1962) The operation was performed with an operating microscope so that the aberrant lashes could be seen sufficiently well One month later the patient was re operated for an entropion like condition of the right lower lid following the first operation A third operation was performed after another two months Plastic surgery of the left upper and lower lid was performed in March 1972 The patient still has trouble in her right eye and the result of the operations is

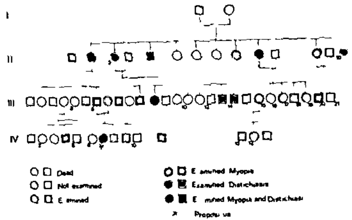


Fig 3

The pedigree of the first family with 31 examined members and 9 cases of distichiasis The propositus is Case 1 The mother's family was also investigated although it is not included in this pedigree Myopia was also found to be inherited in the father's family

Case 4 A. P

The 4? year old daughter of Case 3 (Fig 3 III 8) had no complaints about her eyes Only one additional lash was situated in the temporal part of the left lower lid (Fig 5) It was epilated The son of this patient had myopia but no aberrant lashes

Case 5 M A.

The ?1 year old brother of Case 4 (Fig 3 III 13) had no symptoms Three additional lashes were found in the nasal parts of both lower lids (Fig 6) The aberrant lashes did not irritate the eyes No treatment was given



Fig 4

Three additional lashes in the right lower lid of Case 3



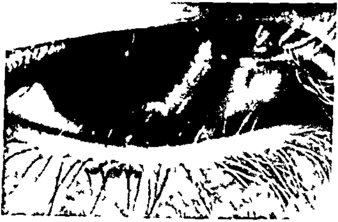


Fig 1
The additional row of lashes in the right lower lid of Case 1

of large areas of myopic degeneration around the optic nerve head and macular pigmentary changes Both lower lids showed two aberrant lashes near the lacrimal punctum They did not rub against the eyeball and there was no irritation of the eyes No treatment was given

Case 3 M A

The 68 year old sister of Case 2 (Fig 3 II 2) had no trouble with her eyes The right eye showed three additional lashes in the lower lid (Fig 4) and two additional lashes in the upper lid The left lower lid had two aberrant lashes No treatment was needed

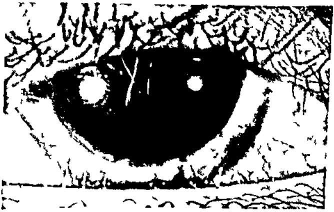


Fig 2
The additional row of lashes in the right upper lid of Case 1

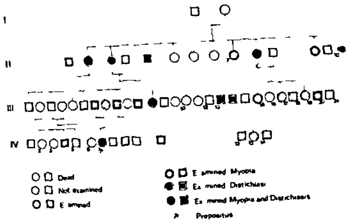


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Fig 4

Three additional lashes in the right lower lid of Case 3



Fig 5
The only additional lash in the left lower lid of Case 4

Case 6 H A

The 21 year old twin brother of Case 5 (Fig 8 III 14) had no symptoms Three additional lashes were found in the nasal parts of both lower lids No irritation was found and no treatment was given

Case 7 V P

The 66 year old brother of Cases 2 and 3 (Fig 8 II 3) complained of irritation in both eyes since his childhood He had occasionally epilated additional irritating lashes but presbyopia had recently prevented this kind of treatment and his sypmtoms had become worse The right lower lid showed 6 additional lashes and the left lower lid four Since some of the aberrant lashes were situated in the middle part of the right



Fig 6
Three additional lashes in the right lower lid of Case 5

lid margin, they rubbed against the cornea The right lower lid was operated with the technic presented by Fox (196) Histopathological examinations revealed normal meibomian glands The aberrant lashes in the left lower lid were treated with electro lysis. He was re examined nine months after the operation and the right lower lid seemed to need a new operation for a cicatricial entropion like condition

Case 8 V K.

The 53 year old sister of Cases 2 3 and 4 (Fig 3 II 8) complained of itching and irritation in both eyes Both lower lids showed 4 additional lashes near the lacrimal punctum and they rubbed against the eyeball This patient declined to have further examinations

Case 9 A. R

The 48 year old sister of Cases 2 3 7 and 8 (Fig 3 II 10) was examined by a col league (Pekka Pohjanpelto M D) The left lower lid showed one additional lash about 4 mm laterally of the lacrimal punctum

FAMILY 2

Case 10 A. M

A 31 year old man came to our outpatient eye clinic because of a minor accident Quite by chance it was found that he had 8 additional lashes in both lower lid mar gins (Fig 7) and two additional lashes in the left upper lid margin He had no symp toms from these aberrant lashes and no treatment was given

Thirty eight members of th s patient s family were examined (his only son his 4 brothers and 4 sisters and their 7 children, his 5 aunts his 6 cousins and their 5 ch ldren his mother and her 5 cousins) His father was dead Two of his sisters four of h s aunts and four of his cousins were myopic No other distichias s was found

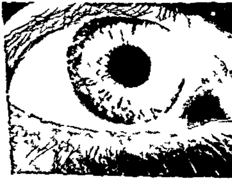


Fig 7
E ght additional lashes in the right lower lid af Case 10

FAMILY 3

Case 11 E S

An 11 year old girl was admitted to our outpatient eye clinic because of diabetes One aberrant lash in the normal location of a meibomian gland was found quite by chance in the left lower lid (Fig 8) No treatment was given Her father was dead Her mother and 5 of her 8 siblings were examined and no distichiasis and only one myopic person was found



Fig 8
The only additional lash in the left lower lid of Case 11

Discussion

This investigation of three families in three generations confirms the view that the mode of inheritance of congenital distichiasis is of an autosomal dominant type with a quite high degree of penetrance It was also found that the inheritance passed over a generation Although the parents had no distichiasis the child had inherited it from one of the grandparents The manifestation was variable The number of the aberrant lashes varied greatly and also the part of the lid margin where they were situated One patient (the first family Case 1) was found to have an additional row of lashes in all four lids The symptoms caused by aberrant lashes also varied to a great extent It seemed better to avoid operations because it was difficult to obtain satisfactory results The condition did not affect the visual acuity Myopia was also found to be inherited in two families Most of these patients with additional lashes showed myopic refraction although no syndrome of distichiasis and myopia can be claimed to exist Histopathological examination revealed that the lid margins contained both normal and atrophic meibomian glands with aberrant lashes

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M S Norn *Demodex folliculorum (the hair follicle mite) in the ocular region* Survey and demonstration of preparations and tables Publ *Acta ophthal (Kbh)* Supplementum 108 Munksgaard 1970

Discussion *S Ry Andersen E Sebber*

433rd Meeting October 24th 1970 jointly with the Ophthalmological Society of Southern Sweden at the University Eye Clinic Lund

N Ehlers and S Ahrons *Corneal transplantation and histocompatibility* Publ. *Acta ophthal (Kbh) 49* 1971 515–527

Discussion *Sv Kessing A Anseth*

K. Wilke *Intraocular pressure measurement on the middle of the cornea and on the limbus*

With a vibration tonometer described by Krakau which has a very small spherical contact surface between the cornea and the tonometer the intraocular pressure was measured in various sites of the cornea on enucleated eyes and on living eyes On enucleated eyes measurements done on the middle of the cornea and tho e done on the l mbus were strongly correlated ($r = 0\ 998$) to the real intraocular pressure measured with an open manometer No significant difference was found between measurements done on the middle of the cornea and on the limbus

On living eyes the measurements done on the middle of the cornea and those done on the limbus were highly correlated ($r = 0\ 96$) to those done on the central part of the cornea with a Goldmann tonometer in 26 patients with intraocular tensions of from 8 to 46 mmHg There was no significant difference between the measurements from the central part of the cornea and those from the limbus in these patients ($r = 0\ 994$)

Intraocular pressure measurements with a vibration tonometer near the limbus proved a valuable method in patients with irregular corneas but a normal limbus in whom the Schiotz or Goldmann applanation tonometer was inapplicable

B Ehinger *Glycine and GABA neuron in the retina*

On pharmacological g ounds a number of substances – besides acetylcholine cate cholamines and ndolamines – have been suggested as neurotransmitt rs in the CNS but glycine and GABA seem to be the most promising ones at present An active neuronal uptake mechan sm has been demonstrated for GABA The exogenously added GABA has bee i shown to be stored in the same pool as endogenous GABA. Provided that diffus on artefacts can be avoided there is thus a possibility of demonstrating pr sumable GABA neurons by autorad ography Freeze drying followed by gas fixa tion and plast c embedding has proved adequate for the purpo e With this technique certain rabbit retinal cells having the position of amacr ne cells become radioactive after the njection of GABA or glycine and there is also a diffuse radioactivity over

TRANSACTIONS OF THE DANISH OPHTHALMOLOGICAL SOCIETY 1970–1971

BY

E GOLDSCHMIDT Secretary

432nd Meeting September 26 1970 in Copenhagen (Eye Department Rigshospitalet Blegdamsvej)

E Gregersen and J Edmund *The new Eye Department of Rigshospitalet Orientation and demonstration of the Department*

K Bech *Thrombosis of the sinus cavernosus with bilateral central vein thrombosis*

Bilateral central vein thrombosis occurred in a 49 year old woman who had a history 4 months prior to the onset of right sided spontaneous fistula of the carotid sinus cavernosus which thrombosed spontaneously Orbitophlebography disclosed thrombosis of the vessels in the right orbit but satisfactory filling of the veins in the left orbit There was good visual remission on the right but not on the left Repeated orbitophlebography 7 months later revealed the development of a number of fairly wide collaterals on the right where previously there had been total thrombosing of the vessels

The case was discussed and the opinion was advanced that bilateral central vein thrombosis is an extremely rare finding in spontaneous thrombosing of carotico cavernous fistulae

Discussion *H Ehlers H Bynke*

N Ehlers *Demonstration of the hemiopic limit in normal subjects by means of an extramacular inhibition phenomenon*
To be published in *Acta ophthal (Kbh)*

Discussion *V Dreyer N Willumsen*

Table I
Operations on the vitreous body

Injection	Air Saline solution Cerebrospinal fluid
Transplantation	Human vitreous Silicone oil Artificial vitreous
Vitrectomy	Cutting of vitreous strings Removal of the entire vitreous

The use of pure hyaluronic acid for replacement of liquid vitreous in retinal detachment cases was first suggested by Balazs on the basis of the idea that hyaluronic acid is a natural agent present in the normal vitreous body and in possession of good transparency a high molecular weight and low toxicity Experiments have shown that hyaluronic acid in a 0 4 % solution has a viscosity of 10 centipoise which is 10 times as much as water The hyaluronic acid molecule has a weight of 150 000 and might be produced in extremely long chains by which the molecular weight in higher concentrations will be brought up to several millions According to Widder 90 % will be reabsorbed in one week while 60 % will be reabsorbed in two weeks In order to inhibit antigenicity the solution was freed of protein and other impurities The principal effect of hyaluronic acid is to inhibit the formation of fibrous tissue in bone cartilage and vitreous This effect of hyaluronic acid on cells is a physiological regulatory mechanism that may be the controlling factor in the movement and multiplication of cells in the cortical layer of the vitreous (Balazs)

In animal experiments higher concentrations of hyaluronic acid seem to demonstrate a certain depressive effect on the basal metabolic rate but in a concentration of 0 2 % no toxicity to the retinal cells could be demonstrated Based on a long series of experiments *Hruby in* 1961 produced Etamucin. The solution is prepared from bovine vitreous and is *stored sterile in* a 2 ml ampoule that can be used for direct injection passing easily through a 23 gauge needle In the present series the dose was from 1 to 4 *ml per injection*

In the majority of cases the injection is performed from below and applied mm from the limbus the needle being introduced through the pars *plana of the* retina When it has passed the wall it is guided by direct ophthalmoscopic control into the correct direction i e at *right* angles to the detachment

This is preceded by a diascleral puncture usually in the lower nasal quadrant The injection is continued until an adequate tension preferably a little more than 30 mm has been attained Sometimes a *blink pulse* has been noted but as a rule it disappears spontaneously within a few minutes In a *couple of aphakic* cases injection through the anterior chamber was tried a technique which has been used previously with silicone oil However this *procedure* cannot be recommended

The material totals 53 cases To illustrate the special character of this material a certain clinical grouping was done (Table II)

the inner plexiform layer which is the synaptic region of the amacrine cells Some ganglion cells also become radioactive but usually less so than the other neurons. Morphological observations indicate that the cells which become radioactive with glycine are different from those rendered radioactive by GABA If the retina is exposed to tritiated aspartic or glutamic acid only the Muller cells and no nerve cells show radioactivity Thus it seems plausible that at least cells having the position of amacrines use glycine or GABA as the transmitter substance Direct comparison with fluorescence micrographs has demonstrated that cells containing dopamine form a different group

Discussion *F Godtfredsen*

J Edmund and Sv Kessing *Injection of hyaluronic acid in the treatment of retinal detachment*

In spite of highly developed surgical techniques for the treatment of retinal detachment a minor group of cases still remains where the retino choroidal contact cannot be established by the usual surgical approach In this group comprising mainly complicated cases surgery on the vitreous seems to be indicated in order to re establish the vitreous cavity

Surgery on the vitreous is not a new invention Injections into the vitreous were started long before the time of Gonin but not until the last ten years have experiments and investigations created the possibility of a reasonable treatment

In Table I these surgical measures are shown in outline The last group will not be mentioned further in this connection while the first two groups will be discussed in more detail The demands on replacement of the vitreous may be set out as follows

(1) The solution must be sterile
(2) It must be sufficiently stable
(3) It must possess a perfect transparency
(4) a viscosity about that of the vitreous and
(5) a molecular weight so high that it will stay in the eye long enough
(6) It must not show any allergenic possibilities or exert any toxic action either upon the intraocular tissues or following reabsorption in the blood stream

With injection of gas the demand for sterility may be difficult to meet but a factor which is even more insufficient is the speed of reabsorption *According to Widder more than 90% of the injected gas disappeared within 6 hours Saline solution* has a viscosity little better than that of water more than 90% will be reabsorbed in less than 24 hours The same applies to cerebrospinal fluid Injections or transplantations of human vitreous from enucleated eyes involve a high risk of infection and the viscosity is not sufficient being only slightly higher than that of water Vitreous transfer sounds encouraging but the demand for viscosity and speed of reabsorption is not sufficiently fulfilled

The use of silicone oil as indicated by Cibis affords certain advantages concerning viscosity speed of reabsorption (which is zero) and transparency but the toxic effect upon the intraocular tissues seems to exclude the use of this material The first indication that hyaluronic acid might be used as a therapeutic agent in certain connective tissues came as early as 1940 when hyaluronic acid injected into a joint was found to prevent the development of adhesive fibrous cartilage tissue between the articular surfaces in the joint

without the use of Etamucin and in Table IV they are assigned to the group of not reattached. It may be seen further that primary cure was more common than permanent cure. Re detachment occurred in most of the cases between the 10th and 14th day after surgery. This might indicate that the time of reabsorption of Etamucin is too short, so that sufficient stability in the retino vitreo choroidal connection has not been achieved by this time. There seems to be an evident agreement between the experimentally demonstrated reabsorption of Etamucin and the occurrence of re detachment in the present material.

In Table III an attempt is made to illustrate the complications and the tolerance of the eye to Etamucin. Vitreous haemorrhage occurred in 4 cases immediately or shortly after the injection. This seems to make for less favourable results. Precipitation and opalescence after one injection occurred in 13 cases but did not seem to be of decisive importance in the process of reattachment. This precipitation thus appears to have no significant influence upon the final result. Surprisingly precipitation or opalescence did not occur more often following repeated injection and intraocular reaction was not observed in any case.

Table III

Complications to and tolerance of Etamucin injections

	Reattached	Not reattached	No of eyes
Vitreous haemorrhage	1	3	4
Opalescence			
one injection	6	7	13
repeated inject	0	0	0 (25)
Intraoc reaction	0	0	0

On the basis of these observations it seems reasonable to conclude that the solution is of sufficient sterility and that its antigenic property must be low which appears to confirm Hruby's statement that the protein content is extremely low. Etamucin apparently has *no* tissue irritating components. Finally the vitreous does not seem to be as delicate as presumed and tolerates surgery quite well. According to these findings it would appear indicated to attack the difficult group of detachment by more intensive surgery on the vitreous and *to try setting up indications for this procedure*. The experience from the present material is listed in Table IV.

In this Table the 53 cases are *divided into three groups*. In the first group extra bulbar surgery was performed at the same time as the injection usually as a localized impression or an encircling procedure. In the second group Etamucin was used as a secondary procedure without simultaneous surgery. In group 3 finally Etamucin injection was the only procedure. The *first group of 37* cases is sub divided into 4 indications. In most of the cases Etamucin was used because neither the impression by

The aphakic group was the largest one comprising 18 cases Owing to the small number of cases no percentages will be given and on the whole this report is not intended to deal in detail with the reattachment in the individual groups The values given must be regarded as indicative and expressive of the special nature of this material However they tend to show that aphakia in an excessively myopic eye has a considerably poorer prognosis than the senile aphakic eye In all ²/₃ of the cases could be cured Thereafter Table II shows the gloomy group of bilateral detachment In all 14 cases the other eye was blind because of incurable retinal detachment It must be considered a good result that almost half of these cases could be cured In the next group excessive myopia, the result is almost the same As a small special group the one of vitreous haemorrhages was analysed This group comprises 7 cases in which the detachment was preceded by a vitreous haemorrhage which obviously is a bad clinical sign Though small this group seems to indicate that the poor prognosis is not due to the bleeding itself but rather to a disease present before haemorrhage occurred This is demonstrated by the fact that both patients with traumatic vitreous haemorrhage achieved a permanent cure whereas none of the others achieved re attachment Finally the results in the total material are given below Permanent re attachment was obtained in almost 40 % of the cases a result in agreement with the 44 % reported by Hruby in his series of 153 cases treated with Etamucin Moreover his range of indications for Etamucin hardly seems as narrow as ours The listing of 3 cases as permanently reattached means that 3 cases achieved recovery by reoperation

Table II
Clinical grouping and results

	Prim reattachment	Sec detachment	Sec reattachment	Perm reattachment	Not attached	No of eyes
Aphakic group						
excess myopic	2	1	1	1	3	4
cong cataract	1	0	0	1	1	2
senile cataract	6	3	4	5	6	11
traumatic cataract	0	0	0	0	1	1
Bilat detachm group	11	9	6	6	8	14
Excess myop group	10	9	6	5	9	14
Vitr haemorrh group						
spontaneous	3	3	0	0	4	4
traumatic	2	1	1	2	0	2
diabetic	1	1	0	0	1	1
Total	36	27	15	20 (17)	33	53

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Table IV
Indications for Etamucin injections

		Reattach	No of eyes
Etamucin inj – simultaneous implant op	hypotonia	9	23
	residual detach	3	9
	giant oral tear	0	4
	uncomplicated	1	1
Etamucin inj – earlier implant op (1–5)		3	12
Etamucin inj – no implant op		1	4
Total		17	53

implant nor tightly encircling cerclage could prevent hypotonia and the situation was unstable In 9 of these cases the retina could be reattached and we have no doubt that this could not have been achieved without the injection In 9 cases residual detachment was noted during the operation and in 1/3 of these cases the injection of Etamucin was able to press back the retina and bring about a permanent cure On the other hand in cases of a *giant tear that is with a completely reversed retina the injection* was ineffective Among 12 cases where from 1 to 5 surgical procedures had failed to result in a reattachment 1/4 were cured by Etamucin injection Finally in the last group of 4 cases in which Etamucin was used as the only procedure the optic media were so blurred that ophthalmoscopy was impossible so that any surgical procedure had to be performed blindly A positive effect was attained in only one of these cases

Conclusion

The indications for injecting Etamucin into the vitreous body may be set up as follows

(1) Maximal hypotonia during the operation
(2) Residual detachment after the application of a local implant or an encircling procedure
(3) Blurring of the optic media so that ophthalmoscopy is impossible and there seems to be no other possibility of a surgical procedure

The experience from this series confirms that injection into the vitreous seems to be much better tolerated than might be expected and that surgery on the vitreous might become a new possibility in treating cases of retinal detachment which have a poor prognosis

Discussion *H Gromall*

C E T Krakau *Improvement and simplification of pupillary aqueous flow measurements*

In measuring the pupillary aqueous flow the aqueous humour has to be stained by fluorescein and the chamber content mixed well The newly formed aqueous is then seen as a clear bubble growing from the pupil The method has been considerably im proved by the introduction of a simple set up for guiding the convection in the an terior chamber By a gentle cold current of air the convection is enhanced and the aqueous is rapidly mixed The convection is then stopped by a warm current and measuring can take place

The latter procedure has been highly simplified After contemplating the shape of photographically recorded bubbles it has proved possible to obtain a significant measure of the bubble simply by measuring two (possibly three) orthogonal diameters of the bubble This can be obtained by putting a measuring grid in the eye piece of the slit lamp microscope and recording the time needed for the bubble to reach certain boundaries This time can be determined with a s d of 9 % in cuvette experiments

M Warburg *Sex linked intermediate retinitis pigmentosa and Mary Lyon s theory*

Eleven men of a Danish pedigree exhibited retinitis pigmentosa In four of the cases their daughters sons had retinitis pigmentosa A sister of 4 of the men had 2 daughters who again had 4 sons all with retinitis pigmentosa None of the men of the pedigree had sons with retinitis pigmentosa There were 12 obligate carriers of retinitis p gmentosa 2 of whom exhibited no signs of the disease whereas the remainder showed varying manifestations Neither the men with retinitis pigmentosa nor the carriers had fundal changes suggestive of chorioideraemia In the carriers the fundal changes were identical in the right and left eye This uniformity is explicable only on the basis of Mary Lyon s theory of accidental inactivation of one X chromosome on the 1?th–16th foetal day presupposing that the ocular primordium is undivided at this stage As the eyes develop from two primordia one on each side of the neural groove it cannot be pure statistical chance that decides which X chromosome is in activated

Discussion *E Goldschmidt*

G Stigmar P Belfrage N O Berg & A Nordén *Crystalloid de posits in the retina and lymph nodes in a patient with night blindness and abdominal pain*

A 30 year old married woman was ad nitted because of abdominal pain A complete gastro intestinal examination afforded no explanation of her complaints For about 12 years she had noticed increasing impairment of night vision There were no signs of itamin A deficiency and no evidence of a general disturbance of the lipid or protein metabol sm A biopsy f om a lymph node which was slightly enlarged revealed a crystallo d material intracellularly in giant cells Extensive chemical analysis f the nature of the foreign material suggested that it might be of lipid nature

Exam nation of the eyes showed slight impairment of central vision in the RE paracentral scotoma of the right visual f eld and complete absence of dark adaptation The optic d scs and retinal vessels appeared to be normal There was an advanced

pigmentary degeneration of the retina and the choroidal vessels were prominent. Some coarse pigment clusters were found, but the most striking observation was a lot of small and highly reflecting spots centrally in the fundus. They had the ophthalmoscopic appearance of crystals but did not look like cholesterol.

At the age of 20 the patient had had gonococcal salpingitis, which had been treated. There were no signs of other venereal infection. However, her general condition was rather poor for a long time. Her E.S.R. remained high. At that time she was believed to be suffering from systemic lupus erythematosus, but this could not be proved. Crystalloid material had been present in the retina then, but less extensively than now. It had been assumed to be of protein nature. The serum level of gamma globulin had been high. At present her serum electrophoresis is almost normal. Both parents and two siblings have normal retinal findings and a normal dark adaptation.

D i s c u s s i o n: *A. O. Berg, H. Ehlers, M. Warburg, C. H. Cronwall.*

S v e n Ö s t e r l i n: *The vitreous in the aphakic eye.*

It is well known that after intracapsular cataract extraction the vitreous will show signs of decreased stability. The incidence of vitreous detachment increases and ruptures of its anterior part are not uncommon, at times showing full blown Irvine's syndrome.

On the basis of the molecular organization of the vitreous body, the stabilizing role of hyaluronic acid in the vitreous gel was explained.

In post mortem studies the author found that in cases where one eye had been subjected to cataract extraction, the vitreous of this eye showed on the whole a lower concentration of hyaluronic acid than that of the non-operated eye. The concentration pattern of hyaluronic acid in the operated eyes indicates that the loss is due to increased diffusion to the anterior chamber.

The loss of hyaluronic acid is presumed to act not only upon the stability of the gel but also upon the biological function of the vitreous as a "molecular sieve" and "shock absorber".

434th Meeting, December 5, 1970, in Copenhagen
(Medical Lecture Room, Rigshospitalet, Blegdamsvej)
Bjerrum Memorial Lecture

Professor D. K l e i n, Geneva: *Clinical associations and genetic classification of chorioretinal abiotrophies.*

435th Meeting, February 12, 1971
jointly with the Society for Illuminating Engineering, in Copenhagen
(Medical Lecture Room, Rigshospitalet, Blegdamsvej)

H. Fledelius *Ultrasound measurement of ocular axial length*

A survey was given of basic ultrasound physics and the practical problems regarding measurement of the dimensions of the various eye components

An ultrasonic study of 48 patients with high myopia had been performed to detect the occurrence of retinal detachment It will be published in more detail in *Acta ophthal (Kbh)*

Discussion **V.** *Clemmesen* demonstrated a handy portable ultrasound equipment which can be used in the field

Erik Frederiksen *Visual conditions on unlighted roads*

The Ministry of Public Works has asked the Danish Illuminating Engineering Laboratory whether it would be preferable to use a light coloured or dark coloured paving on motorways or in other words which retroreflection should be prescribed for road surfaces on motorways

According to the classical opinion of the contrast cond tions on an unlighted road an object on the road will appear lighter on a darker background In this case the contrasts – and consequently the visual conditions – would improve if a dark surface were used

This is contrary to the current views so that it was decided to carry out an investigation to elucidate some of the problems connected with the named conditions

The maximum possible visual distance (the critical visual distance) to an object on the road is of essential importance to safety when driving on an unlighted road Therefore the critical visual distance is a relevant way of describing the visual conditions

The critical visual distance is influenced by a number of factors among others the ability of the road surface to reflect the light from the headlights back to the driver (the retroreflection of the surface)

The purpose of the investigation was to determine the influence of the retroreflection of the road surface on the critical visual distance

A laboratory model scale 1 8? was built and measurem nts of the critical visual distance were made in a number of different situations

In add tion to a theoret cal investigat on on the contrast conditions in the said situati ns and on the basis of the fundamental data concerning the contrast sensitivity of the eye (Blackwell) a mathemat cal model for the calculation of the critical visual distance has been developed

Comparison of the measured with the calculated values of the critical v sual distance shows sl ght systemat deviat ons but even so the mathematical model is applicable for making a reasonably accurate estimate of the influen e on the critical visual d stanc exe ised by the retroreflection of the road surface and certain other factors such as the size and the reflection factor of the object

Comparison of the results reported by other authors with those obtained by the s id mathemat cal mo lel shows in most cases a good correlation but in a few rather marked discrepanc es are seen An explanation of these d screpancies has not been found

The onclusion of the nvestigat on is that the minimum critical visual distance to an object with an arbitrary reflection factor increases with increasing retroreflection of the road u face It was found also that the difference between the critical visual

distances to objects with different reflection factors was least on roads with a high retroreflection

In practice this means that dark and light objects can be seen at approximately the same distance on a light road whereas a dark object on a dark road can be seen only at a considerably shorter distance than a light object on a dark road or a dark object on a light road This effect is most pronounced in dealing with small objects because the critical visual distance to objects higher than the horizon depends only to a lesser extent on the reflection properties of the road surface

The investigation has later been extended by a study carried out for the Council for Road Safety Research

The aim of this extended investigation is to determine the effect of glare as well as the driving speed on the visual distance to objects on the road Its results will be published

Jens Gudum *Visual conditions on lighted roads*

H W Larsen *Photocoagulation in retinal diseases*

First the object principles and technical details of photocoagulation using the Zeiss photocoagulator were presented

Thereafter the indications and contra indications for photocoagulation in the treatment of fundus diseases were discussed and the therapeutic results were illustrated by retinal photographs

It was concluded that photocoagulation therapy may be indicated (1) for further closure of retinal tears after successful operation for retinal detachment (2) for closure of retinal holes in the absence of retinal detachment (3) in juvenile retinoschisis to restrict the splitting up to the retinal layers (4) in retinal angiomatosis (5) in Eales disease (6) in Coats disease and (7) in early stages of proliferative diabetic retinopathy and in selected cases of non proliferative diabetic retinopathy

The contra indications to photocoagulation therapy were stated to be (1) existing retinal detachment (2) retinal cysts (3) extensive retinoschisis (4) late stages of proliferative diabetic retinopathy (5) malignant melanoma of the choroid and choroidal metastases

In retinoblastoma photocoagulation should not be employed as the only treatment but rather as adjuvant to e g mobaltron therapy

The range of indications for photocoagulation is overlapped by that for laser therapy In the future photocoagulation therapy using the Zeiss photocoagulator will presumably be replaced by treatment with Argon laser or some other form of laser

J Edmund *The Ruby laser and its therapeutic use in ophthalmology*

The basic principles of the laser light were outlined and the construction of the Ruby laser described

The applicability of the 6943 Angstrom Ruby laser beam was pointed out the range of its use discussed and compared with the Argon and Neodymium lasers

Finally the clinical indications for the Ruby laser were set out by means of some cases of macular lesions in which the therapeutic effect of the laser beam was demonstrated

436th Meeting March 13 1971 in Copenhagen (Copenhagen City Hospital)

S v K e s s i n g *A new microsurgical operation for glaucoma (trabeculotomia ab externo)*

The operative and postoperative complications as well as the preliminary results of ab externo trabeculotomy by the method of Harms were reported for a series of 18 glaucoma operations

The material compris s cases with buphthalmos juvenile glaucoma Sturge Weber s disease aniridia and glaucoma simplex

Schlemm s canal was located in all but 4 cases

Except for negligible corneal injury in 2 cases there were no operative complica tions

There were no postoperative complications except for fairly persistent hyphaema in two cases and temporary choroid detachment in one Three developed fistulation blebs

In 10 of the 13 patients followed for at least one month after the operation the tension was ≤ 0 mmHg One of these 10 patients is recieving supplementary antiglaucomatous med cation but in a lower dose than prior to the operation

It it concluded that ab externo trabeculotomy by the method of Harms is a procedure which causes little traumatization and has given satisfactory primary results

There is reason for its continued use and collection of postoperative data to elucidate further its final value

D i s c u s s i o n I *Clemmesen*

J A F a h m y *Symptoms and signs of intracranial sacculated aneurysms with a pa ticular view to retinal haemorrhages*

The cl nical symptoms and signs in 154 cases of ruptured sacculated aneurysms were reported It was demonstrated that next to unconsciousness (76 %) and neck rigidity (53 %) retinal haemorrhage is the third most common sign (37 %) Next in frequency are hemiparesis (27) alteration of the level of consciousness (25 %) *facial palsy* (13 %) papilloedema (13 %) and paresis of ocular muscles (8 %)

It is suggested to classify the fundal haemorrhages into grades mild retinal haemor rhages *being* designated as grade I moderately severe cases with marked retinal haemorrhages as grade II and severe cases with preretinal or vitreous haemorrhages as grade III

A finding of even small retinal haemorrhages in pat ents who have suddenly lost consciousness with or without *neck rigid ty is* almost pathognomonic of subarachnoid haemorrhage and ind cates arteriographic investigation

(To be publ shed n more deta l in *Acta ophthal (Kbh)*

N W i l l u m s e n *Insulin act vity in the aqueous humour*

Th m chan sm of diabet c cataractogenesis is still not clear in spite of much ex pe ime tal w k Some v dence points to the probab l ty that hyperglycaemia is the n tial toxic fact r for th lens (*Patterson 1953*) Recent work by Farkas & Weese (19 0) has sugg st d a physiological role of insul n in the glucose metabolism of the lens These find ngs indicate that the lack *of insulin* in the aqueous humour could be a contr buting factor n the development of d abetic cataract Such a hypothes s must

be based on the presence of physiological concentrations of insulin in the aqueous humour of non diabetic subjects

The present study is concerned with measurements of insulin activity in the aqueous humour Aqueous from 6 healthy bovine eyes and from 6 human eyes with uncomplicated senile cataract was drawn by puncture Assay of insulin activity was performed by the isolated fat cell method (Gliemann 1965) using triplicate measurements and parallel controls with anti insulin sera (kindly carried out by J Gliemann MD Inst Med Physiol C University of Copenhagen) A micromethod was developed which reduced the necessary amount of aqueous to about 20 μl This made measurements on samples from single eyes possible The minimum sensitivity of the method approximated 2 μU insulin per ml

Insulin activity could not be demonstrated in any aqueous humour whether bovine or human A statistical evaluation showed no significant disparity from insulin free test solutions (*t test for paired comparison* $P > 0.1$ $n = 8$)

It is concluded that a physiological role of insulin in the lens metabolism is questionable As a consequence insulin does not seem to be a direct pathogenetic factor in diabetic cataract

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Farkas T G & W C Weese (1970) *Exp Eye Res* 9 132
Gliemann J (1965) *Acta physiol scand* 72 481
Patterson J W (1953) *Amer J Physiol* 172 77

M S Norn *Vital staining of the cornea and conjunctiva by iodonitrotetrazolium*

Vital staining by iodonitrotetrazolium (1 % *aqueous solution*) is particularly appropriate for demonstrating bacterial conjunctivitis (the mucous thread stains diffusely red owing to a high content of neutrophilic leukocytes) and for demonstrating chronic conjunctivitis simplex (punctate staining of the tarsal conjunctiva) Compared with rose bengal it must be concluded that iodonitrotetrazolium is a reliable vital staining which stains abnormal structures in particular unlike rose bengal which also stains structures that may occur in normals (e g mucus)

This subject has been discussed in more detail in two papers

(1) Iodonitrotetrazolium vital staining of cornea and conjunctiva (*Acta ophthal (Kbh)* 49 90–102 1971) and

(2) Enzyme activity in the conjunctival mucous thread (*Acta ophthal (Kbh)* 49 525–538 1971)

S Jensen & F Goldschmidt *Genetic counselling in sporadic cases of congenital cataract* *Acta ophthal (Kbh)* 49 572–576 1971

457th Meeting April 17 1971 at Scanticon near Arhus
Bjerrum Memorial Lecture

Claes Dohlman Boston *Advances in the treatment of corneal diseases*

Discussion *Prause P Barford St Kessing C Fouphier M S Norn T Bertelsen N Willumsen*

438th Meeting April 17–18 1971 at Scanticon near Århus

A Anseth *Wound healing in keratoplasty*

In principle there is no difference between the process of healing in a perforating corneal wound and the process of healing which unites a graft with the host cornea in a penetrating keratoplasty

The area of the wound swells because lacrimal fluid and aqueous humour get absorbed through the cut surface This swelling combined with precipitation of fibrin in the wound helps to prevent leakage from the wound

The epithelial cells of the graft soon disappear and cells from the host cornea gradually cover the anterior opening of the wound and the naked surface of the graft

The endothelial cells of the graft survive and the posterior surface of the wound gets covered by adjacent cells which divide by mitosis The edges of Descemet s membrane fuse by newly formed membranous tissue

The stability of a corneal wound develops much more slowly than e g in a skin wound The explanation of this phenomenon possibly is lack of blood vessels Dohlman and his associates have demonstrated that peripheral corneal wounds heal more rapidly than more central wounds This shows that also the distance to the vascular bed influences the rate of healing

A fascinating aspect of the process of wound healing is that which concerns the biochemical and histological changes taking place in that part of the corneal stroma which makes up the healing zone

Normally the corneal stroma consists of delicate collagen fibrils of an even diameter arranged in lamellae regularly on top of each other The polysaccharide content of the ground substance differs greatly from that found in other connective tissue especially with respect to the relatively large content of keratan sulphate

The polysaccharides are believed to be operative in the transparence of the cornea among other things by regulating the content of fluid in the corneal stroma

In the swollen edges of a perforating corneal wound there will be a marked loss of polysaccharides up to about 50% of the normal content New formation of keratan sulphate does not appear to take place in the non transparent scar tissue On the other hand dermatan sulphate has recently been isolated from corneal scar tissue This polysaccharide does not occur in the normal corneal stroma This finding is interesting because dermatan sulphate occurs normally in connective tissue in which the collagen fibrils are coarse and of an irregular arrangement as in the skin and sclera i e very like the collagen which forms in a corneal scar

Very little is known about the relationship between dermatan sulphate and collagen *in vivo* but it is not unlikely that the presence of dermatan sulphate affects the formation of collagen fibrils of varying diameter

We also do not know which cells synthesize dermatan sulphate in the scar tissue It may be the white blood cells which arrive in the area of the wound 5–6 hours after the injury However the emigrated cells are not normally capable of synthesizing dermatan sulphate so that it seems unlikely that these cells from the blood stream are responsible for the production of this polymer A more attractive theory is that the keratocytes which are similar to fibroblasts in the area of the wound have been transformed in some way or other to dermatan sulphate producing cells

Many interesting problems remain to be solved in connection with wound healing in the corneal stroma At present we can merely state that the process of wound healing

transforms the highly specialized corneal stroma to a more primitive type of connective tissue lacking the most important biological property of the cornea viz its transparence.

Discussion *N Ehlers C Dohlman*

N Ehlers & S Ahrons *Corneal transplantation and histocompatibility Acta ophthal (Kbh) 49* 513–527 1971

J Edmund *Corneal grafting in the acute stage*

In corneal grafting in the acute stage always on therapeutic indications the lines set up by Paufiques were followed The present series of 55 cases was divided into 3 groups *Group 1* in which the operation was done to save the eye *Group 2* in which it was done because conservative treatment had failed *Group 3* though not actually belonging under active surgery comprises cases of recurrent lesion in which prophylactic surgery was performed and is well suited for a comparison with the results of surgery in the acute stage

The bulk of the series belongs to group 3 which is almost twice as large as groups 1 and 2 together In assessing the results of corneal grafting not only the phase in which surgery is performed but also the cause of the disease is highly important Two phases in the postoperative course were distinguished viz the immediate postoperative phase representing the time from the operation until the sutures were removed and the second phase i e the time from the removal of the sutures and up till now Within each group the results are divided according to whether a lamellar or a penetrating procedure was applied

The final conclusion from this material may be stated as follows In cases of spontaneous perforation with a descemetocele the results appear to show that surgery is always indicated even though the final result is merely saving the eye with impaired visual acuity

In acute corneal disease surgery is indicated when permanent cure of recurrent disease has not been achieved after a suitable period of observation According to the present series lamellar grafting appears to be the preferable surgical procedure although a penetrating graft may give a good final result Especially in recurrent dendritic keratitis it seems worth considering lamellar transplantation at a not too advanced stage In the majority of cases this operation seems to protect the patients from recurrence and in quite a number it improves vision

P M Møller & J Hvidberg Hansen *Lamellar keratectomy by the method of Gundersen*

To be published in *Acta ophthal (Kbh)*

Discussion *Wille Jorgensen T Bertelsen*

N Willumsen & N T Rosenberg *Band keratopathy treated with EDTA*

After gentle removal of the epithelium EDTA 2 5 % is instilled every 2–5 minutes

In most cases the subepithelial depositions of calcium may be completely removed by such fractionated treatment continued for 1½–2 hours

The indications for this procedure are (1) discomfort due to recurrent erosions (2) cosmetic (3) visual

Three cases with photographic documentation were submitted

E. Osterby *Postoperative treatment of pterygium by thiotepa*

Thiotepa is a mitosis inhibiting agent of the nitrogen mustard type It is applicable postoperatively in pterygium

The reported recurrence rate after postoperative thiotepa therapy is as shown in Table I

Table I

	No of patients	Recurrence	Rate of recurrence %
Meacham	30	1	3
Mori (1969)	31	5	16
Cassady	17	0	0
Liddy & Morgan	26	1	4
Joselson & Muller	46	9	4
Vitali	50	3	6
Portney	64	12	19
Mori (1960)	89	11	13
Saliev	31	1	3

In the Eye Department of the Odense University Hospital a consecutive series of 45 patients treated during the period 1963–19 0 showed the recurrence rate apparent in Table II

Table II

Thiotepa	No of eyes	Recurrence	Rate of recurrence %
+	30	2	6
–	17	9	12

Thus on the basis of this study it is not possible to draw any final conclusion as the difference *is not significant* but the figures might suggest some favourable effect of postoperative thiotepa therapy On the other hand there was a distinct inhibition of postoperative vascular ingrowth into the cornea

Table III

Thiotepa	No of eyes	Vascularized healing
+	8	2 (7)
–	15	4 (7 %)

Discussion *M S Norn F Goldschmidt*

H Skydsgaard *Flush fitting lenses*

Discussion *E Gregersen C Dohlman*

C H Mordhorst & C R Dawson *Neonatal inclusion conjunctivitis*
To be published in the *Amer J Ophthal*

H H Seedorff *Linear cataract extraction using vacuum*
Linear extraction of loose lens masses by suction has been recommended recently by several authors as a gentle procedure often affording a quicker visual improvement than the conventional discission procedure This should considerably reduce the risk of among other things amblyopia in children

However the instruments used so far have proved unsatisfactory clumsy and difficult to employ

A foot operated suction control which can be connected to the central suction in the operating theatre was demonstrated By this apparatus it is possible to vary the suction satisfactorily At the same time both hands are free one to place the needle through which the suction is performed and the other to fix the eye by forceps

Four cases treated satisfactorily by this procedure were described

Discussion *H Skydsgaard V Dreyer P barfoed*

K K Dreisler *Rapid discharge following cataract operation*
A material of 241 cataract operations performed in the Central Hospital Holbæk by the same surgeon during a period of 2 years 3 months was analysed for complications It was investigated whether these complications might be related to the anaesthetic method the suturing technique and/or the length of time spent in the hospital after the operation About half the patients were discharged 4–6 days after the operation the others after a varying length of time down to 1 day after the operation

The complications were as follows

1 case of expulsive haemorrhage necessitating enucleation

4 cases of iridic prolapse treated by re suturing

1 case of epithelial cyst in the anterior chamber removed by excision of the cyst and iridectomy

2 cases of flattened chamber with choroid detachment which subsided spontaneously

1 case of vitreous loss in a patient with excessive myopia

1 case of pupillary block despite peripheral iridectomy abolished by sector iridectomy

2 patients required discission because of capsular rupture followed by a secondary pupillary membrane

All the operations were carried out using operation microscope and cryotechnique the great majority under general anaesthesia A total of 195 eyes were sutured by various single sutures ranging in number from 3 to 10 Forty five eyes were sutured by continuous 10–0 nylon sutures from Messrs Klein of Heidelberg This suturing method which is new in Denmark was demonstrated by diapositives from the Holbæk Hospital and by a film borrowed from Professor Boke of Kiel

No complications of any kind occurred in the 45 eyes sutured by continuous sutures

in spite of the short time spent in hospital after the operation a day or two in a number of cases

As might be expected the occurrence of iridic prolapse could be related to disturbed awakening from the general anaesthesia too small a number of single sutures and the patient s lack of self control during the postoperative period but proved to be un related to the length of time spent in hospital

Conclusion By continuous 10–0 nylon sutures operation microscope cryotechnique and a good general anaesthesia the length of time spent in hospital after cataract operation may safely be reduced to a day or two

M S Norn *Vital staining of corneal endothelium in cataract extraction*
Acta ophthal (Kbh) 49 725–733 1971

Discussion *C Dohlman*

TRANSACTIONS OF THE SWEDISH OPHTHALMOLOGICAL SOCIETY

EDITED BY

ILMARI RENDAHL, M. D.

Meeting in Falun, March 20, 1971

SYMPOSIUM ON EXOPHTHALMOS

B. Tengroth: *Introduction.*

G. Prame: *Retrobulbar tissue in endocrine exophthalmos.*

Our knowledge about the retrobulbar tissue in endocrine exophthalmos is based mainly on animal experiments. Only a few cases of human retrobulbar tissue have been investigated.

The immediate cause of the protrusion of the eye in endocrine exophthalmos is an increase in the bulk of retrobulbar soft tissues. This increase is due mainly to an increased water content of the retrobulbar tissue. In human endocrine exophthalmos also a hypertrophy of the outer eye muscles contributes to the increase in volume of the retrobulbar tissue. The cause of the orbital oedema has generally been attributed to an increase in mucopolysaccharides of the retrobulbar connective tissue. This concept has been based on results obtained by methods not specific for mucopolysaccharides. On the basis of separation and characterization of the mucopolysaccharides of the retrobulbar connective tissue in fish, chromatographic micromethods were chosen and adapted for studies of this tissue in experimental exophthalmos. It could be shown that the mucopolysaccharides in experimental exophthalmos in fish did not change either quantitatively or qualitatively. Also the content of collagen, as measured by hydroxyproline, did not change. The characteristic change of the retrobulbar tissue was instead an increase in the content of glycoproteins. This increase was on the whole proportional to the degree of the exophthalmos. As the orbit of fish even normally contains a small amount of free retrobulbar tissue fluid, a comparative study of this fluid was done with normal fish and fish with exophthalmos. It was found that the concentration of proteins in the retrobulbar tissue fluid in fish with exophthalmos was increased

and that this increase was principally accounted for by small protein molecules especially albumin The results correspond best with an increase in permeability of the orbital capillaries in endocrine exophthalmos This increased permeability causes a leakage of fluid and low molecular proteins to the retrobulbar space and leads to the orbital oedema

L Frisén *Exophthalmos measuring problems*

The most important problems of clinical exophthalmometry are the poor correlation between measuring values and degrees of orbital overfilling and the large normal variation In spite of their greater importance these problems have attracted far less attention than problems of precision

The poor correlation with orbital filling can be improved by paying attention to the position of both the eye bulb and the peribulbar tissues (extended exophthalmometry[1]) A photoelectric technique capable of such measurements has been described previously it is particularly useful for individual monitoring

The normal variation can be reduced by using additional information with a high correlation to the normal measuring value An X ray skull base size index has been used profitably for this purpose[3] A search for equally useful but more easily measured parameters is desirable

S Almqvist, P Algvere & E Backlund *Malign endocrine exophthalmos*

To be published in *Acta ophthal (Kbh)*

T Jerndal & Kerstin Norrsell *Pneumoorbitography and orbital venography in cases of unilateral exophthalmos*

Two different methods for examination of the orbit are discussed viz pneumoorbitography and orbital venography We have used these techniques in cases of unilateral exophthalmos and they have proved of great value where other techniques have failed

Two cases are presented Case I a 40 year old man suffering from exophthalmos on the right side Routine X ray including angiography of the internal carotid artery was negative Pneumoorbitography and orbital venography showed a process in the upper medial part of the orbit Surgery confirmed the diagnosis and a hemangioma was excised

Case II a 67 year old man who suffered from complete ophthalmoplegia of the right eye Orbital venography showed obstruction in the posterior part of of the superior ophthalmic vein indicating a thrombosis The clinical picture could tally with a thrombosis in the cavernous sinus

G Swegmark *A case of lymphatic leukaemia with orbital reticulo sacroma*

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[1] Frisén L (19( ) *Acta ophthal (Kbh)* 4) 631

[2] Frisén L (1965) *Nord Med* 79 197

[3] Tengroth B Bergen H & Zackrisson U (1964) *Acta ophthal (Kbh)* 4 864

Meeting in Stockholm, November 27 1971

A Holmberg *Combined keratoplasty and cataract extraction*
(To be published in *Acta ophthal (Kbh)*)

M Rydberg *Binocular vision in unilateral aphakia corrected with contact lens*
(To be published in *Acta ophthal (Kbh)*)

K G Nyman *Treatment of amblyopia in young children with extrafoveolar fixation*

K G Nyman *Bifocal lenses in children with accomodative squint*

G Aurell *Orthoptist training in Sweden*

S Stenkula & R Tornquist *Retinal tears and retinal detachment in Eales disease*

Since 1961 64 eyes in 39 patients have been observed and treated for Eales disease at the Eye Clinic in Örebro Retinal neovascularisations in these eyes have been treated with light coagulation

Most of the eyes showed a vitreous detachment and in many of these eyes we noticed firm vitreoretinal adhesions In 7 eyes we found a retinal break but no retinal detachment The tears which generally were of the horseshoe type were treated with light coagulation All eyes were healed but one eye developed retinal tears and a retinal detachment half a year later The operation with cryopexy and scleral indentation was then successful Five eyes had retinal holes and retinal detachment Four eyes were successfully treated with cryopexy and a scleral buckling operation One eye was not operated as the detachment was too old Two eyes had retinal detachment but no retinal breaks In these eyes there was a massive vitreous contraction In one eye an encircling operation was tried but with no effect

Conclusion

Retinal holes and retinal detachment are common in Eales disease Of our cases 20 % showed retinal breaks and 10 % showed retinal detachment The high rate of retinal complications is probably explained by the development of firm adhesions between the vitreous and the inflamed retinal vessels preceding a vitreous contraction which is often found in these cases The retinal breaks are successfully treated with lightcoagulation Some of the retinal detachments are of the rhegmatogenous type and in these cases cryopexy and a scleral buckling operation are usually successful Some of the retinal detachments are combined with a vitreous contraction and they have a poor prognosis

I Magnusson S Stenkula & R Tornquist *Diagnostic problems in angiomatosis retinae*

I Anjou *An unusual case of craniopharyngioma*

B Bengtsson *On so called normal values in tonometry*
(To be published in *Acta ophthal (Kbh)*)

S D Alani *Diagnosis of periorbital eczematous dermatitis and allergic conjunctivitis by patch testing*

Patients with contact eczema or allergic conjunctivitis were patch tested routinely with the suspected allergens during two years in the eye department Central Hospital Karlskrona Most of the patients were suffering either from glaucoma or from chronic conjunctivitis and were on topical treatment for a long or short time The other group of patients were allergic to different kinds of cosmetics and household chemicals A special routine patch test series for patients with glaucoma has been used This series consists of the active substances (e g adrenaline pilocarpine and anticholine esterases etc) conservatives antioxidants and vehicles found in antiglaucoma preparations Rubber chemicals and plastics of the eyedrop containers were also included

The concentrations of some substances not used previously in patch testing were determined by systematic patch testing on healthy volunteers

The other group of patients were tested with the used preparation as it is and with its constituents The cosmetics were applied as they are

By the application of patch test technique in this investigation the specific allergen in many cases of suspected contact allergy could be determined with certainty

The causative allergen can be a known allergenic substance such as neomycin or could be an unexpected rare allergen such as hydrocortisone prednisolone adrenaline mintacol or Di iso propoxy phosphoryl fluoride (DFP) Even the conservatives in eye drops such as benzalkon chloride phenyl mercury acetate and sodium pyrosulfite can be the causative allergenic substance Eczema due to household chemicals such as polishing oils soaps washing powders or insecticides is not infrequently encountered which is also the case with cosmetics

Patch testing proved to be an adequate diagnostic method for example in patients with glaucoma who are on different combinations of eyedrops therapy where it is difficult to detect the causative substance(s) of allergy

Therefore routine patch testing performed by a well trained person is a helpful diagnostic method in cases of contact allergy in ophthalmology

l Anjou A *vacuum pillow as head support in eye surgery* (with film demonstration)

E Linner *Point sampling technique for quantitative analysis of the retinal circulation in the intact human eye*

Methods for measuring the retinal circulation as accurately as possible are of great physiological and clinical importance Fluorescein angiography was used for measuring the circulation time and estimating relative changes in retinal blood flow The purpose of the method presented below is to improve the analysis of the retinal circulation in the intact human eye by using a point sampling technique

The black and white fundus pictures taken during fluorescein angiography were magnified about 10 times The area of the visible vessels was estimated by using the point sampling technique (H W Chalkley *J nat Cancer Inst 4* 47 1943 H Elias A Henning & D E Schwartz *Physiol Rev 51* 158 1971 B Hellman *Acta Endocrin 1 3 9 19*)) By moving a simple pattern of 8 points at *regular intervals* over the picture and summing up the number of points lying on or outside the vessels filled with fluorescein the distribution of these points becomes proportional to the area of the vessels within the area examined On each enlargement 576 points were counted in the preliminary study Fundus pictures were taken at suitable intervals in order to determine the movement of fluorescein within the retinal vessels By using a time interval as short as about 0 1–0 seconds between two subsequent pictures during the

very early arterial phase the movement of fluorescein within the central retinal arteries could be measured and used for estimating the total retinal blood flow in an undisturbed eye During a late phase the retinal vascular volume could be estimated in different retinal parts separately which can be of clinical interest in localized circulatory disturbances The method can also be useful for other problems such as determining the total area and the average area of microaneurysms in cases of diabetic retinopathy Thus a quantitative analysis of certain diabetic lesions can be made more accurately than by following the changes in numbers of aneurysms from time to time as described in previous reports (E Linnér *Nord Med 69* 653 1963 K E Rasmussen *Acta ophthal (Kbh) 44* 641 1966)

In preliminary examinations the method was used in three patients two of them being examined on two different occasions A part of the posterior fundus around the disc and macula was analysed During the early phase of filling there was an average increase in the fluorescent vascular area of 4 per cent per second The apparatus available at this time could not be used for taking fundus photographs at very short intervals and therefore no attempt was made to estimate the blood flow In a late phase the fluorescent area of the retinal vessels occupied about 30 per cent of the posterior fundus It was possible to observe vessels with a diameter of about 30–40 μ

JUDICIA DE NOVIS LIBRIS

Okun E Johnston G P & Boniuk I Management of Diabetic Retinopathy A stereo scopic presentation C V Mosby Saint Louis 1971 Price US$ 50 75

This book is based on the authors wide experience in treatment of diabetic retinopathy It starts with a review of the development of diabetic retinopathy and the complexity of its various elements and continues with an extensive classification of diabetic re t nopathy usable for scientific purposes Finally a survey is given on the treatment o diabetic retinopathy including medical therapy Xenon photocoagulation Argon photo coagulation pituitary ablation and scleral buckling in diabetic retinal detachment

It is concluded that photocoagulation in most instances is the therapy of choice

Every chapter contains many black and white fundus pictures illustrating th various cond tions mentioned in the text Reels with stereoscopic fundus pictures i color illustrating the conditions described are affixed to the inside back cover alon with a portable viewer and allow the reader to study the stereoscopic pictures concur rently with the text

This book is highly recommended to all ophthalmologists and especially to thos treating diabetic retinopathy

Hans Walther Larsen

Dartnall H J A Handbook of Sensory Physiology Vol 7 Part 1 Photochemistry Vision Springer Verlag Berlin Heidelberg New York 1972 810 pages 2 f gures Price Cloth DM 238 US $ 74 10 Subscription price Cloth DM 190 4 US $ 59 30

This is the first of four parts compris ng volume seven of this comprehensive han book Volume seven deals with all aspects of the physiology of the visual system T present initial part of this volume conducts i s reader in 18 chapters each written an expert in the part cular field through the whole complex of problems concern the photochemistry of vis on Starting with the interaction of light and matter d sc ibes the visual p gments and their chemistry as well as the visual cells of t whole animal kin dom from invertebrates to man treated from both taxonomic a ecological standpo nts Every chapter is absolutely up to date even unpublished d re quoted Often a summary at the end of a chapter greatly increases the value of format on given n t to ment on the extensive l st of references con luding ea hapter The reproduction of electron micrographs are at a high level and the ma sket hes and diagrams everal eproduced from lead ng journals are illustrative T lay out and the typog aphy are of the usual very pleasant qual ty produced by Spr nger V rlag

The aim f the ed t s was to provide a source book for the research worker T aim is exc llently full lled This first part s and no doubt its successors will mandatory f e e y laborat ry and department where research on vision a d on ual rg n and pathways is going on

O A Jensen

Stein H A & Slatt B J The Ophthalmic Assistant Fundamentals and Clinical Practice C V Mosby Saint Louis 1971 4/0 pages Price $ 22 50

Undoubtedly the ophthalmic assistant will enter into the daily life of eye patients to an increasingly greater degree both in private practices and in hospitals In order for eye specialists to be able to meet their own obligations and those of furthering the field of ophthalmology it will be necessary for them to delegate those techniques and skills which can be carried out by others

In many places and for many years to come it will still not be possible to give ophthalmic assistants a formalized education inasmuch as they simply will have to learn on the job For these ophthalmic assistants and the doctors who supervise them this particular book is a gold nugget which can be instrumental in creating competent and effective assistants

The first five chapters discuss the eyes anatomy physiology optics pharmacology and microbiology The following chapters cover refraction technique eyeglasses contact lenses visual field technique and assisting in operations Hereafter the way is paved for more special procedures such as tonography photography of the eye and examination of squint eyed patients The book concludes with a review of commonly used eyedrops as well as an ophthalmologic glossary and a 16 page subject index

The illustrations are abundant extremely instructive and well chosen The text is easy to understand and enjoyable This book is simply *the* cookbook for ophthalmic assistants and deserves inclusion in the fixed inventory of each and every ophthalmologic office and department where auxillary personnel are employed

E Crevcersen

Warburg Mette Diagnosis of Metabolic Eye Diseases Munksgaard International Publishers Copenhagen 1972 112 pages Price D Kr 115 00

The metabolic eye diseases constitute a dynamic group of illnesses inasmuch as biochemical conquests in the past few decades in innumerable areas have brought about changes in classification simultaneous with the considerably improved possibilities for making the correct diagnosis

This particular book thus fills a great need inasmuch as it is formed both as a survey and as a reference work It is extremely easy to use since the subject matter is organized by location of the various ocular metabolic disturbances These locations (the eye as a whole the eyelid muscles conjunctiva cornea sclera lens the vitreous body the retina and the optic nerve) are stated at the top of each page and act as an automatic topographic universal key throughout the entire book

Under the pertinent ocular localization and the main morphological diagnosis the applicable biochemical categories are stated in each case For every single disease the ocular changes are listed in detail as well as the general findings followed by a short description of the specific metabolic disturbances laboratory findings pathology genetics and possible treatment as well as finally the relevant references from the last decade The book concludes with a subject index totalling 10 pages

This book is not only an easy quick much needed brush up but is also a knowledgeable concise easily accessible guide to the greatly expanded labyrinths of metabolic diseases and as such can be most highly recommended as a worthwhile purchase for each and every eye specialist

F Crevcersen

From the Department of Ophthalmology
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NEW COMPRESSION TESTS IN GLAUCOMA

I. Simplified bulbar pressure technique and biomicroscopical compression test

BY

A. P. NESTEROV, E. K. CHURBANOVA and A. I. KOLOTKOVA

Two new diagnostic techniques based on the compression of the eye are described. The simplified bulbar pressure test includes the compression of the eyeball through the upper eyelid by a finger for three minutes and subsequent analyses of the intra-ocular or volume changes. The test proved to be useful for the early detection of chronic glaucoma.
The biomicroscopic compression test is based on the difference in the reaction of the aqueous veins to the compression of the globe with the force of 30 to 50 g for three minutes. During this period of time the aqueous veins are dilated in normal eyes and tend to be filled with blood in eyes with primary open-angle glaucoma.

Key words: diagnosis of glaucoma – bulbar pressure test – aqueous veins – compression of the eye

Compression tests are used to evaluate the *facility of aqueous outflow* and aqueous inflow. Although a number of modifications of the compression test techniques are described (Bock, Kronfeld & Stough 1934; Vurgaft 1952; Blaxter 1953; Rosengren 1956; Krasnov 1957; Sobanski, Swietliczko & Szosland

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1957 Koslov 1964) many ophthalmologists do not employ them in routine practice because the techniques are too complicated and of insufficient diagnostic value The aim of this paper is to describe two new procedures which proved in practice to be of value in evaluating aqueous dynamics

Simplified Bulbar Pressure Test

In order to work out the simplified technique of the bulbar pressure test for routine clinical practice several series of investigations were carried out

The relationship between the compression force and volume decrement of the eyeball (ΔV) was studied in 28 normal eyes in 28 persons The globe was compressed with Baillart ophthalmodynamometer for three minutes The tip of the ophthalmodynamometer was applied to the temporal part of the globe The Maclakov tonometry was performed before and after the compression of the eye The value of ΔV was calculated making use of the calibration table for the Maclakov tonometer (Nesterov & Vurgaft 1972) Each eye was compressed with the force of 30 g 50 g and 70 g during three successive days at one and the same time of the day The volume decrement was equal to $11\ 68 \pm 3\ 08$ mm³ (mean ± standard deviation) after compression of the globe with the force of 30 g $11\ 64 \pm 3\ 38$ mm³ when the pressure force was 50 g and $11\ 36 \pm 3\ 93$ mm³ under the influence of the pressure with the force of 70 g Earlier analogous results were reported by Kozlov (1964) for compression of the eyeball with the force of 30 g and 50 g

Thus for practical purposes there is no need to exert an exact force of external pressure on the globe It needs only to be in the range between 30 and 70 g

The outside pressure on the eyeball with the ophthalmodynamometer is transmitted to the orbital contents and the pressure in the orbital veins is likely to increase This factor is eliminated if a suction ophthalmodynamometer is used

In 22 eyes of 22 healthy persons the compression test with the ophthalmodynamometer (30 g) was performed as described above The next day the procedure was repeated but the suction technique was used instead After tonometry was performed the cup (inside diameter 7 8 outside diameter 9 mm) was applied to the temporal segment of the globe The negative pressure of 190 mmHg was applied After three minutes the cup was removed and tonometry was performed again It had previously been found that the increment of the intra ocular pressure was the same with both techniques used The mean values and standard deviations of ΔV were identical with both procedures $14\ 15 \pm 2\ 30$

mm³ and 14 15 ± 2 11 mm³ respectively The role of the pressure change in the orbit during the compression test seems to be negligible

Grant & English (1963) pointed out the possibility of the evaporation of the aqueous humor through the cornea during tonography To examine the possible influence of this on the results of the bulbar pressure test the following investigations were performed On 62 healthy persons the bulbar pressure test was performed (50 g 3 minutes) with both eyes open On the fellow eye which was not compressed the decrease of the intra ocular pressure was equal to 2 09 ± 0 78 mmHg In 25 healthy persons the same procedure was performed but both eyes were closed and the outside pressure (50 g 3 minutes) was applied through the upper eyelid No change was observed in the intra ocular pressure in the fellow eye Before and after the test it was equal to 16 2 ± 2 01 mmHg In 78 persons the intra ocular pressure was measured after epibulbar anesthesia with ¼ % solution of dicain Then the patient was requested to look straight ahead After 5 minutes the tonometry was repeated The intra ocular pressure decreased to 1 94 ± 0 81 mmHg Thus the evaporation of aqueous humor seems to change the result of the bulbar pressure test if the eye is open during the time that the test is performed

The application of the external pressure through the eyelid is less trouble some for the patient Nevertheless the compression load is usually applied directly to the globe because it is unknown what part of the applied force is absorbed by the resistance of the eyelid In 15 persons the compression force with the ophthalmodynamometer was applied to one eye in both ways at first to the sclera and then through the upper eyelid just beneath the superior edge of the orbit The tonometry was performed before and immediately after the outside pressure was applied When the latter technique was used the incre ment of the intra ocular pressure diminished slightly The mean differences were equal to 1 92 ± 0 81 mmHg with the compression force of 30 g and 2 01 ± 0 86 mmHg with the force of 50 g The force required to overcome the resistance of the eyelid is about 5 g

In 27 healthy eyes the bulbar pressure test (50 g three minutes) was per formed through the upper lid with the ophthalmodynamometer The procedure was repeated the next day at the same time of the day However the eyeball was pressed by the finger of the examiner instead of the ophthalmodynamome ter Both techniques gave the same results The mean value of ΔV was equal to 10 51 ± 2 00 mmHg after the compression test with the ophthalmodynamo meter and 10 72 ± 1 94 mmHg when finger pressure was applied

On the basis of the data presented above the following technique has been elaborated for the bulbar pressure test After tonometry the examiner puts his finger on the upper eyelid just beneath the orbital margin and presses the

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Table I

Results of the biomicroscopical compression test in normal and glaucomatous eyes

Test result	Normal eyes		Open angle glaucoma		Closed angle glaucoma	
	No	Per cent	No	Per cent	No	Per cent
Negative	262	93.6	6	3.2	62	58.5
Mildly positive	6	2.1	51	26.8	12	11.3
Positive	12	4.3	133	70.0	32	30.2
Total	250	100	190	100	106	100

The aqueous veins became filled with blood in only 4.3 % of normal eyes and in 30.2 % of 106 eyes with chronic closed angle glaucoma as well as in 0 % of 190 eyes with primary open angle glaucoma In patients with primary open angle glaucoma the test was positive or mildly positive in the early cases It was not so in patients with primary angle closure glaucoma the test being positive only in the advanced cases of the disease and negative in the early cases

Sixty two eyes of the 42 glaucoma suspects were examined Negative results were obtained in 29 eyes After complete examination of the patients in the hospital closed angle glaucoma was found in nine cases and open angle in two eyes The mildly positive test was observed in 6 eyes Primary open angle glaucoma was established in four of them the others were left for further observations The test proved positive in 14 eyes Primary open angle glaucoma was established in 10 of them In the other four cases the condition was not clear

The comparison between the results of the biomicroscopic test and tonography was made in 157 eyes The C values were 0.13 ± 0.052 mm³/min/mmHg (the mean ± standard deviation) in eyes with the positive test 0.17 ± 0.072 mm³/min/mmHg in cases with the mildly positive response and 0.29 ± 0.113 mm³/min/mmHg in the eyes with the negative test Thus there was a certain correlation between the results of tonography and of the biomicroscopic compression technique However it should be noted that in individual cases considerable differences between the results of both procedures were encountered

eyeball slightly It is possible for the examiner to check the pressure force on his own eye A compression force of less than 30 g is almost not felt and if the force is more than 70 g one usually feels some discomfort or even pain The compression of the globe lasts for three minutes and then tonometry is repeated In 156 normal eyes of 100 persons aged 25 to 76 years (mean 44 5 years) the following diagnostic criteria were established (1) the ΔV value must not be less than 6 5 mm³ (2) the decrease of intra ocular pressure ($\frac{\Delta P_o}{P} \times 100$) in normal eyes is $\geq 30\%$

In 52 eyes of 40 patients with an early open angle glaucoma and intra ocular pressure below 22 mmHg the data obtained with the bulbar pressure test were compared with the results of clinical tonography The coefficient of aqueous outflow facility was ≤ 0.15 mm³/min/mmHg in 31 eyes (60 %) $P_o/C \geq 100$ in 40 eyes (77 %) and the positive bulbar pressure test in 46 eyes (88 %) Thus the bulbar pressure test as a diagnostic procedure seems to be more effective than tonography This can be explained both by the unequal compression load and by the different positions of the applied force as regards the iris lens diaphragm

Biomicroscopic Compression Test

A biomicroscopic compression test is performed in the following manner With the help of a slit lamp the aqueous or laminar vein is sought out The eye is subjected to pressure by the ophthalmodynamometer through the upper eyelid with a force of 30 to 50 g It was found possible to press the globe by a finger instead of the ophthalmodynamometer The compression of the globe and observation of the aqueous vein lasts for three minutes Under the influence of the outside pressure the aqueous vein is dilated and the flow of liquid along it is intensified If increased flow in the aqueous vein can be observed during all the time of compression the test is considered to be a negative one The result of the test was considered to be positive if in the course of the time in spite of the constant compression of the globe the rate of aqueous flow diminished and the aqueous vein became filled with blood

In some cases the result of the test was uncertain Neither the intensification of the aqueous flow through the vein nor the blood filling phenomenon occurred We considered such a response of the aqueous vein to be mildly positive

The test was carried out in 280 normal eyes of 172 persons from 18 to 84 years of age (mean 41 years) and on 296 eyes of 185 patients with primary glaucoma The results are given in Table I

Table II
V values Calibration scale for Maclakov tonometers (10 g)

D mm³	V mm	D mm³	V mm	D* mm³	V mm
4.0	0.0	5.5	18.9	7.0	38.5
4.1	1.3	5.6	20.3	7.1	40.0
4.2	2.5	5.7	21.8	7.2	41.6
4.3	3.7	5.8	23.1	7.3	43.1
4.4	4.9	5.9	24.6	7.4	44.7
4.5	6.1	6.0	26.0	7.5	46.9
4.6	7.4	6.1	27.2	7.6	48.1
4.7	8.6	6.2	28.3	7.7	49.7
4.8	9.9	6.3	29.6	7.8	51.3
4.9	11.2	6.4	30.8	7.9	53.1
5.0	12.5	6.5	32.0	8.0	54.8
5.1	13.7	6.6	33.3	8.1	56.6
5.2	14.9	6.7	34.5	8.2	58.3
5.3	16.[illegible]	6.8	35.8	8.3	60.5
5.4	17.4	6.9	37.3	8.4	62.7

* Diameter of the applanated area

Kolotkova (1969) established that the blood filling phenomenon depended both on the value of the compression force and on the duration of its application

A biomicroscopic compression test is based on the above mentioned investigations Our data testify that this test is a useful procedure for early detection of the chronic open angle glaucoma The advantage of the test is that it is independent of calculations and possible consequent errors

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Discussion

In this study the ΔV-values were constant if the external pressure applied to the eyeball was within the range of 30 to 70 g The cause of this is unknown The mean intra ocular pressure increment was equal to 24 mmHg for a pressure of 30 g 36 mmHg when the compression force was 50 g and 46 mmHg for a force of 70 g The fact that the ΔV values were constant may be explained either by the proportional increase in the pressure of the episcleral and intra scleral veins or by the decrease of aqueous outflow facility The first cause seems unlikely as similar results were obtained with both the Baillart ophthal modynamometer and the suction technique

An important point which must be considered is the correctness of the cali bration tables used for the intra ocular pressure and the intra ocular volume We have employed the tables for the Maclacov tonometer which were adopted by the Board of the All Union Society of Ophthalmologists in 1971 (Nesterov & Vurgaft 1972) The P_t values were derived from experiments performed on 10 isolated eyes The volume of the displaced aqueous humor (V_c) was cal culated by the method described earlier by Goldmann & Schmidt (1957) Then the P_0 and the ΔV values ($V_c + V_s$) were calculated using Friedenwald s equation for P_0 (Friedenwald 1937) and Grant s equation for ΔV (Grant 1950) The coefficient of ocular rigidity was taken to be equal to 0 02 The ΔV values are given in Table II

These calibration tables were checked by Kiselev & Tanjashina (1972) In each eye they determined the C value by the Maclakov tonometer and the Schiotz electrotonometer and measured the intra ocular pressure by the Gold mann applanation tonometer and the Maclakov tonometer Good correlations were found between the data obtained by these tonometers although noticeable differences were detected in several cases

Taking into consideration the above investigations one can hardly say that the results described in this paper depend on the peculiarities of the calibration tables for the Maclakov tonometer Our modification of the bulbar pressure test (Vurgaft 1952) seems to be the simplest among all the other analogous tests and of equal diagnostic value

Compression of the globe causes the widening of the aqueous veins and acceleration of the aqueous flow through them (Ascher 1942) Kleinert (1951) showed that if the compression force is great enough the aqueous veins can be filled with blood The value of the external pressure which is necessary for this phenomenon to occur was called compensation maximum" The author found the value of the compensation maximum" to be less than 100 g in glaucomatous eyes However this is true only for advanced cases of glaucoma

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ULLRICH TURNER SYNDROM MIT ARCUS AORTAE DEXTER OPHTHALMOLOGISCHEN UND ANDEREN MISSBILDUNGEN SOWIE FAMILIÄRER KOMBINATION MIT MARMORKNOCHENKRANKHEIT

VON

U HEINE und H BÖRNER

Bei einer zwanzigjährigen Patientin mit Ullrich Turner Syndrom wird auf die Anhäufung vielfältiger Missbildungen hingewiesen Die Zugehörigkeit in diesem Falle zu einem Ulrich Turner Syndrom wurde durch die Chromosomenanalyse exakt nachgewiesen Die hier beschriebene familiäre Kombination eines unseres Wissens erstmalig vorgekommenen Ullrich Turner Syndroms mit bei Zwillingen diagnostizierten Marmorknochenkrankheit ist unseres Erachtens in der Literatur noch nicht beschrieben worden Auf die Bedeutung einer frühzeitigen Behandlung wird hingewiesen

Key words Ullrich Turner's Syndrome – chromosomal aberrations – heredity malformations – optic nerve – choroid – retina – coloboma

Bei jedem Mädchen bzw jeder »Frau« mit Kleinwuchs und Hypogonadismus insbesondere primärer Amenorrhoe sollte immer *an ein Ullrich Turner* Syndrom gedacht werden (Sundermann 1965) Auf Grund der Erfolge auf dem Gebiet der Hormonforschung ist das Erkennen des *Krankheitsbildes* heute nicht nur von wissenschaftlichem Interesse Dem Gynäkologen ist es möglich eine symptomatische Hormontherapie durchzuführen Auch der Ophthalmologe

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massig weiter Mamillenabstand erwahnt Cubitus valgus gehort als klassisches Symptom zum Krankheitsbild Die Patienten zeigen uberaltert und schlaff wir kende Gesichtszuge mit herabhangenden Augenlidern und Mundwinkeln (»Sphinxgesicht) Agenesie bzw Dysgenesie der Gonaden ist von grosser diag nostischer Bedeutung

Auf Grund der chromosomalen Geschlechtsbestimmung lassen sich drei Un terformen unterscheiden

1 Falle mit weiblichem Habitus und negativem (mannlichem) Geschlechts chromatin

2 Falle mit weiblichem Habitus und positivem (weiblichem) Geschlechts chromatin

3 Falle mit mannlichem Habitus und negativem (mannlichem) Geschlechts chromatin

Im Harn ist meist eine gesteigerte Gonadotropin und gelegentlich auch eine verminderte 17 Ketosteroidausscheidung nachzuweisen Fakultative Begleit missbildungen werden beschrieben in Form von symmetrischen Veranderungen des medialen Tibiakondylus im Sinne des Blount Syndroms Anomalien des Herz Gefass Systems sowie multiplen Nierenmissbildungen Zumeist wird von normaler oder nur wenig unterdurchschnittlicher Intelligenz berichtet (Leiber & Olbrich 1962 Sundermann 1965)

Als Augenveranderungen werden ovale Hornhaute (Wilkens) Uveakolo bome Papillenfehlbildungen Epikanthus Hypertelorismus Ptosis und Exoph thalmus beschrieben Selten kommen auch Strabismus Katarakte und Pigment mangel der Netzhaut vor (Badtke 1961 Leiber & Olbrich 1962 Thomas et al 1969)

Eigene Beobachtungen Es handelt sich um eine zwanzigjahrige Patientin (Poliklinik Nr 10 723/70) Sie ist das zweite Kind aus erster Ehe Bei dem alteren Bruder besteht eine Aortenstenose (valvular angeboren durch Herz katheter gesichert) Von den drei Stiefgeschwistern aus zweiter Ehe ist nur das alteste Kind gesund Die heute siebzehnjahrigen Zwillingsstiefbruder leiden an Marmorknochenkrankheit (Albers Schonberg) Die Diagnose wurde 1961 in der Universitats Kinderklinik Leipzig (Direktor Prof Dr sc med S Liebe) auf Grund einer Anaemie und typischer rontgenologischer Knochenbefunde gestellt und durch die Universitats Kinderklinik Rostock (Direktor Prof Dr sc med J Reich) durch welche die Kinder in den letzten Jahren betreut wurden be statigt Augenarztlicherseits wurde bei beiden lediglich eine mittelgradige Hyperopie beiderseits diagnostiziert wahrend Pietruschka bei seinen Fallen von Marmorknochenkrankheit Exophthalmus Optikusatrophie und Strabismus

sollte »daran denken« da ihm gelegentlich die Patienten schon vor der Diagnosestellung wegen der mit dem Syndrom vergesellschaftet vorkommenden Augenveränderungen vorgestellt werden Leiber & Olbrich definieren in dem von ihnen herausgegebenen Wörterbuch der klinischen Syndrome das Ullrich Turner Syndrom als eine besondersartige Intersexform mit Chromosomenaberration (gonosomale Monosomie) Es ist den Formenkreisen des Gonadendysgenesie Syndroms und des Bonnevie Ullrich Syndroms zuzuordnen

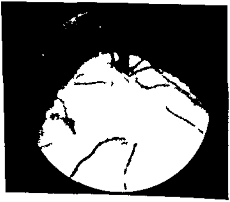
Im Jahre 1768 hat Morgagni als wahrscheinlich erster die Ovarialagenesie beschrieben Von Šereševski sind Arbeiten aus dem Jahre 1928 zu dieser Problematik bekannt (Leiber & Olbrich 1962) In den Jahren 1930 bis 1938 veroffentlichte Ullrich Arbeiten über gemeinsames Auftreten von Pterygium colli Beweglichkeitsdefekten im Hirnnervengebiet (III VI VII, XII) Muskeldefekten (Pectoralis major) lymphangiektatischen Ödemen Mamillenhypoplasie und Syndaktylie (Ullrich 1930 1938) Zur ätiopathogenetischen Erklarung fur dieses Missbilrungssyndrom ubernahm er den Mechanismus der wandernden Liquorblasen von Bonnevie (1935) 1938 wurde von Turner ein neues Syndrom mit Infantilismus Pterygium colli und Cubita valga vorgestellt Elf Jahre danach unterscheidet Ullrich bezugnehmend auf seine Arbeiten von 1936 zwei Formen des Status Bonnevie Ullrich Er trennt die asymmetrischen Formen deren Genese er mit der Blasentheorie Bonnevie s zu erklaren versucht von den endokrin bedingten symmetrischen Formen (Badtke 1961) 1934 wies Ullrich allerdings bereits auf den Zusammenhang der Gonadenagenesie mit dem Bonnevie Ullrich Syndrom hin (Leiber & Olbrich 1962) Albright arbeitete im Jahre 1942 ebenfalls an dieser Problematik

Als Synonyma fur das Turner Syndrom werden folgende Bezeichnungen gebraucht Turner Albright Syndrom Albright Turner Syndrom Morgagni Turner Albright Syndrom Morgagni Turner Syndrom ovarieller Zwergwuchs Ovarialagenesie Gonadenagenesie Gonadendysgenesie pterygonuchaler Infantilismus pterygogonadaler Infantilismus webbed neck syndrome (Turner Albright) Sereševski Turner Syndrom (Leiber & Olbrich 1962)

Das klinische Bild des Ullrich Turner Syndroms ist gekennzeichnet durch die drei klassischen Symptome Pterygium colli Cubitus valgus und Kleinwuchs die mit ausserordentlich vielfältigen Missbildungen insbesondere mit verkummerten Gonaden kombiniert sein konnen Zusammenfassend seien die am haufigsten beschriebenen pathologischen Veränderungen genannt Das Pterygium colli bilaterale ist zwar *charakteristisch aber kommt nicht obligat vor* Der tiefe nuchale Haaransatz wird oft beobachtet Vom Genitalbefund sind die betroffenen Individuen meist weiblich Es liegt ein dissoziierter Infantilismus vor Ein proportionierter Minder oder Zwergwuchs mit verzogertem Epiphysenschluss wird beobachtet Oft werden multiple Thoraxdeformitaten und uber



Abb 1



Abb

divergens beschrieben hat (Pietruschka 1958) Die Mutter der Patientin konnte nach insgesamt funf Schwangerschaften während zweier Ehen nur ein gesundes Kind zur Welt bringen Aus der Familienanamnese ergibt sich kein Anhalt fur ernsthafte Erkrankungen weder bei den Eltern der Patientin noch ihrer beider Aszendenz Augenerkrankungen wurden in der Anamnese ebenfalls nicht angegeben Von Interesse scheint uns das gleichzeitige familiäre Auftreten von Marmorknochenkrankheit und Ullrich Turner Syndrom zu sein In der Literatur ist ein solches familiäres Zusammentreffen dieser beiden Syndrome unseres Wissens noch nicht beschrieben worden Eine genetische Erklärung dafur erscheint zunächst selbst hypothetisch nicht möglich Bei der Albers Schonbergschen Erkrankung sind im Gegensatz zum Ullrich Turner Syndrom auch keine Chromosomenaberrationen bekannt (Becker 1964)

Vom Vater der von der Marmorknochenkrankheit befallenen Kinder sowie seiner Vorfahren sind ebenfalls keine schweren Erkrankungen bekannt Augenarztlicherseits war die Anamnese auch stumm Die Grosseltern der Zwillinge väterlicherseits waren eine Verwandtenehe eingegangen Es handelt sich um die Verbindung zwischen Cousin und Cousine

Nach einer komplikationslosen Geburt verlief die fruhkindliche Entwicklung unserer Patientin verzogert Sie lernte mit 4 Jahren laufen und zwischen dem 5 und 6 Lebensjahr sprechen Das Seh und Horvermogen sei immer schlecht gewesen Nach neunjahrigem Schulbesuch wovon 5 Jahre die Sonderschule fur Horgeschadigte besucht worden war erreichte die Patientin nur das Ziel der 3 Klasse Die Zwanzigjahrige erscheint wie ein etwa zehnjahriges debiles Kind (Abbildung 1) Die Turnersche Trias Pterygium colli Cubitus valgus und Kleinwuchs (Grosse 1 45 m Gewicht 31 kg) lasst bei Fehlen der sekundaren Geschlechtsmerkmale und primarer Amenorrhoe an ein Ullrich Turner Syndrom denken Kurzer Hals mit tief in den Nacken reichendem Haaransatz tief sitzende Ohren und angedeutete Lippenspalte bei hohem Gaumen verstarken diesen Eindruck

Augenarztlicherseits wurde ein typisches ektatisches Funduskolobom mit Stufenbildung beiderseits nachgewiesen (Abbildung [illegible]) Die Tiefe der Ektasie betragt rechts und links bis maximal 10 bis [illegible] dpt Die Kolobomstelle die im oberen Grenzbereich die untere Halfte der Papille mit einbezieht nimmt zur Peripherie hin an Breite zu und ist unten abgerundet Es handelt sich also um ein Optikus Aderhaut Netzhaut Kolobom beiderseits Bei regelrechten Verhaltnissen an den vorderen Augenabschnitten und am Augenhintergrund fiel beiderseits eine antimongoloide Lidspaltenstellung auf Die Bulbi waren frei beweglich Die Hornhaut erschien glatt klar und spiegelnd Fur eine ovale Cornea bestand beiderseits kein Anhalt Die Vorderkammer erschien beiderseits klar und von normaler Tiefe Die Iris war reizfrei

Es bot sich kein Anhalt fur das Vorliegen einer Dysgenesis mesodermalis iridis Die mittelweiten zentrisch gelegenen Pupillen reagierten auf Licht und Konvergenz regelrecht Die in loco gelegenen Linsen waren klar Ein Strabismus bestand nicht Der Augeninnendruck lag beiderseits im Normbereich Die Gesichtsfeldaussengrenzen waren intakt Mit einer Korrektur von [illegible] 1 0 sph comb + 8 0 cyl A 90 wird rechts ein



Abb 1



Abb 2

Fernvisus von 0 5 und mit + 1 0 cyl A 90° links von 0 7 angegeben Der Nahvisus be tragt beiderseits Nieden I/30 cm Entfernung Eine Prufung des Farbensinns war nicht moglich

Auffallig war bei der klinischen Untersuchung eine Blutdruckdifferenz zwischen den Armen bei mehreren Kontrollen Am rechten Arm wurde ein Druck von 100/60 Torr maximal 115/70 Torr gemessen Bei zeitweilig nicht messbarem Blutdruck am linken Arm wurde ein maximaler Blutdruck von 90/70 registriert Über dem Herzen war ein mittellautes mesosystolisches Spindelgerausch mit p m uber S_4 zu horen Im EKG fand sich ein Sinusrhytmus mit Linkspositionstyp Die Farbstoffverdunnungskurve er gab keinen Hinweis auf einen hamodynamisch wirksamen Shunt Es fand sich keine sichere Fehlerform des Herzens Die angiographische Untersuchung ergab als Ursache der Blutdruckdifferenz den sehr seltenen Befund eines Arcus aortae dexter (Abbildung 3) (Oberarzt Dr med J Schulz Radiologische Klinik der Universitat Rostock Direk tor Prof Dr sc med F Held Abteilung fur Rontgendiagnostik Leiter Prof Dr sc med W Moldenhauer kardiovaskulare Abteilung) Alle biologischen Reaktionen wa ren unauffallig so auch das Addis Sediment und PbJ sowie die Kreatinin Clearance Die i v Pyelographie ergab den Verdacht einer hypoplastischen Niere links (Abbildung 4) Dieser Befund konnte auch durch die Nierenszintigraphie bestatigt werden

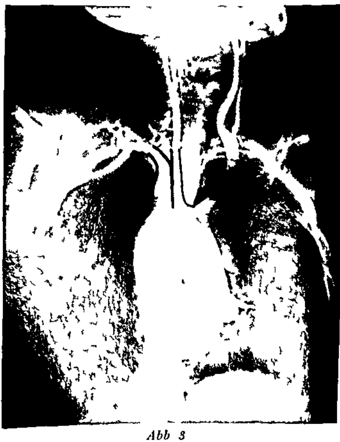


Abb 3



Abb 4

Das Knochenalter entsprach bei der Zwanzigjahrigen dem im 13 bis 14 Lebensjahr Als Nebenbefund konnte ausserdem ein Fehlen der zwolften Rippe links festgestellt werden Die Herabsetzung des Horvermogens ist durch eine beidseitige Innenohr schwerhorigkeit mit starker Schalleitungskomponente bedingt Es handelt sich vermut lich um eine Mittelohrmissb ldung Der Vestibularis war thermisch unerregbar (Uni versitats Hals Nasen Ohren Klinik Rostock Direktor Prof Dr sc med H Dietzel)

Seitens der Universitats Frauenklinik Rostock (Direktor OMR Prof Dr sc. med H Kyank) wurde ein Fehlen der sekundaren Geschlechtsmerkmale festgestellt die Portio uteri sei sehr kle n der Uterus stellte sich als kle ner medianer Strang dar und die Ad iexen seien nicht zu tasten.

Die Chromo omanalyse ergab ein Mosaik vom Typ 46 XX/45 X Der X Chromatin test war entsprechend pos tiv (Abbildung 5) (Dr Pelz Univers tats Kinderklinik Rostock D rektor Prof Dr sc. med J Reich) Die Östrogenausscheidung lag mit 8 bzw 9 / g unterhalb der Normgrenze Die Gonadotropin Ausscheidung ist mit 2,5 MUE in 24 Stunden erniedrigt (Hormonlabor Leiter Dr rer nat hab I C. G Dassler Universitats Frauenklinik Rostock Direktor OMR Prof Dr s med H Kyank)

Fernvisus von 0 5 und mit + 1 0 cyl A 90° links von 0 7 angegeben Der Nahvisus be tragt beiderseits Nieden I/30 cm Entfernung Eine Prufung des Farbensinns war nicht möglich

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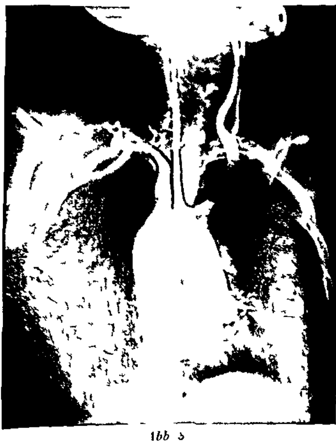


Abb 3

Die Missbildungen konnen sich beim Ullrich Turner Syndrom in mannigfaltigster Art kombinieren Wenn auch nur mit Hilfe der Chromosomenuntersuchung eine exakte Diagnosestellung moglich ist sind dennoch eine Vielzahl von medizinischen Fachrichtungen an ihr beteiligt Auch verschiedene Augenerkrankungen werden bei diesem Syndrom immer wieder beschrieben Der Ophthalmologe sollte an die Existenz dieses hier beschriebenen Krankheitsbildes denken und eine fruhzeitige Überweisung in die Fachkliniken insbesondere zum Gynakologen bewirken Durch eine nicht zu spat begonnene hormonelle Substitutionstherapie kann in gewissem Grade dem Kleinwuchs entgegengewirkt werden Die sekundaren Geschlechtsmerkmale sind in befriedigendem Ausmass zur Ausbildung zu bringen Es bedingt dies eine Steigerung des subjektiven Wohlbefindens und der korperlichen Leistungsfahigkeit Unter diesen Bedingungen beobachtet man oft bei den Patienten eine Starkung des Selbstbewusstseins Sie werden kohabitationsfahig und heiraten oft (Kepp & Staemmler 1971)

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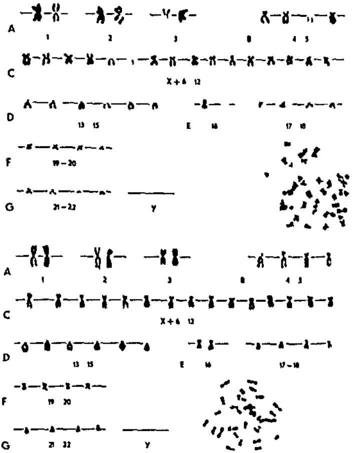


Abb 3

Das Pneumoencephalogramm ergab eine deutliche Erweiterung mit Asymmetrie des Ventrikelsystems im Sinne eines Hydrocephalus internus massigen Grades (Universitats Kinderklinik Rostock damaliger Direktor OMR Prof Dr med habil H Kirchmair)

Die Patientin ist auf Grund ihres Geistes und Korperzustandes nicht arbeitsfahig Sie wurde bereits invalidisiert Seitens der Universitats Frauenklinik Rostock (Direktor OMR Prof Dr sc med H Ky..nk) ist eine hormonelle Behandlung eingeleitet worden Nach den Aussagen der Mutter haben sich in der Folge die sekundaren Geschlechts merkmale in geringem Ausmass ausgebildet und Regelblutungen eingestellt Der All gemeinzustand sei besser und die Patientin fuhle sich unter der Therapie wohler

From the Department of Ophthalmology
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DEFECTIVE DISSOCIATION OF ACCOMMODATION AND CONVERGENCE IN DYSLECTIC CHILDREN

BY

ELSE HAMMERBERG and M S NORN

Accommodation was measured in 78 dyslectic children of whom 21 gave abnormal or subnormal readings These were given a thorough orthoptic investigation which showed 1 accommodative insufficiency 2 convergence deficiency 3 defective visual acuity in one or both eyes for near in spite of 6/6 at 6 m in the majority of the cases *The investigation showed defective dissociation of accommodation and convergence* Fifteen accepted the offer of treatment. Through orthoptic treatment they all improve and 13 could be discharged as orthoptically satisfactory

Key words insufficiency of accommodation – dyslexia – congenital word blindness – reading difficulties – the accommodative effort syndrome

One of the authors of this paper has previously participated in examinations of dyslectic children attending a school for dyslectic children only – Hyldegaards skolen Gentofte Denmark (Norn et al 1969a) Later this investigation was followed by an examination for suppression by means of Jampolsky s Four Prism Dioptre Test (Norn 1969b) The aim of the present investigation was to find out if accommodation was normal in the dyslectic child An accommodative fatigue would add to their reading difficulty so it was decided to measure the Near Point of Accommodation binocularly as well as monocularly

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25 Rostock – DDR Rembrandtstr 18

Therapy

The treatment was the same as in the ordinary convergence deficiency patient The number of treatments given was 6–/

Of the 15 children who accepted the offer of treatment two gave up before treatment was completed one of whom showed signs of improvement

Eleven out of 13 showed normal accommodation after treatment 2 showed accommodation slightly below normal for their age in one eye One is an anisometrope – the other showed a marked latent divergence on cover test with slow recovery of the eye with the subnormal accommodation

After a few treatments the near point of convergence as well as accommodation became normal as is seen in the ordinary convergence deficiency patient In spite of that they all had difficulty in seeing the stereograms clearly When given diploscope excercises they all had difficulty in seeing letters clearly in all four positions When dissociation of convergence and accommodation was mastered diploscope exercises and stereograms became easy

Some of the children volunteered the information that before treatment they had had a feeling of straining their eyes to see print clearly The more they tried the more blurred it became

Defective dissociation of accommodation and convergence seemed to be the main problem and probably the cause of accommodative insufficiency with the secondary convergence deficiency

All children could be discharged as orthoptically satisfactory but still with dyslectic complaints

Discussion

The finding of this not uncommon accommodation effort syndrome in such a high percentage (27 per cent) of the dyslectic children seems to us to prove the importance of an orthoptic investigation in these children and adequate orthoptic treatment when needed It is important to eliminate all obstacles to clear vision and thus make easier the difficult task of reading

We do not find a small hypermetropic refractive error (+ 1 50 D Sph under cycloplegia) significant and consequently we do not order glasses in these cases Where glasses had already been prescribed the use of these weak corrections was discontinued

On the other hand we do *not* believe that there is a connection between dyslexia and defective dissociation of accommodation and convergence

Material

The investigation was carried out on 78 children at Hyldegaardsskolen This school receives dyslectic children only The children are admitted after 2 years in an ordinary school in which the second year is spent in a class specially for children with reading difficulties During this year children with reading difficulties other than dyslexia are sorted out

Method

Accommodation was measured on the Royal Air Force Near Point Rule The test was performed three times binocularly as well as monocularly in order to detect the presence of fatigue

The criterion for offering treatment was a reading of 10–11 cm N 5 or worse (normal for that age group = 6–8 cm)

Investigation

Of 78 children 21 showed signs of an accommodative insufficiency

Only 3 of the 21 patients showed signs of accommodative fatigue thus indicating that we were not dealing with cases of ordinary accommodative fatigue

These 21 children were given a thorough orthoptic investigation Eight children had normal *near point of convergence* i e 6 cm as measured on the Royal Air Force Near Point Rule 13 gave measurements varying from 10 to 23 cm

Fifteen children accepted the offer of treatment

Measurement of accommodation in the 15 children showed that 6 could see the N 5 line binocularly as well as monocularly but the reading was not according to age Some of them gave readings of approximately 25 cm In 9 children the accommodation of one eye varied from N 8–N 12

Only 2 of the 15 had a normal near point of convergence Before treatment the fusion range was good in only 4 cases

Visual acuity in 6 was 6/6 at 6 m and 33 cm In 9 cases visual acuity was 6/6 at 6 m but < 6/6 both binocularly and monocularly or < 6/6 either binocularly or monocularly

Therapy

The treatment was the same as in the ordinary convergence deficiency patient The number of treatments given was 6–7

Of the 15 children who accepted the offer of treatment two gave up before treatment was completed one of whom showed signs of improvement

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SYSTEMIC STEROIDS AND OCULAR FLUID DYNAMICS I

Analysis of the Sample as a Whole Influence of Dosage and Duration of Therapy

BY

V GODEL V FEILER OFRY and R STEIN

Sixty patients treated for various systemic diseases with long term steroids of varying dosages and durations showed a significantly higher mean applanation pressure than both a normal control group and litera ture populations There was no significant difference between these groups for tonographic C values before drinking water but lower values for C and higher values of the log of the Po/C ratio were found in the steroid group after water drinking Cumulative per cent frequency plots for ap planation pressures of the steroid patients revealed an obvious deviation to the right from a straight line in the upper end of the curve starting at the point of 60 % representing patients with pressures of 20 mmHg or higher Presence of a higher mean applanation pressure and absence of an adequately reduced outflow facility in the systemic steroid group are interpreted as evidence of an increased formation of aqueous humor in individuals treated with steroids by this route Analysis of the influence of dosage and duration of treatment disclosed that differences in the mean applanation pressure between these subgroups were not due either to dura tion or dosage of treatment but to the presence or absence of *individuals* within the group responding to steroids with an increase of pressure The proof of this fact will be presented in the second part

Key words intraocular tension – aqueous dynamics – steroids

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Table II
Age and sex of patients in the steroid series

Age	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Total
Males	1	2	6	4	4	6	3	2	28
Females		5	3	4	7	4	8	1	32
Total	1	7	9	8	11	10	11	3	60

ocular diseases or surgery or suffering from secondary glaucoma were excluded from this study

Each patient was submitted to a complete eye examination including biomicroscopy and perimetry Intraocular pressure was measured by applanation and tonography was done before and after water drinking Only technically perfect tonograms were evaluated All cases with eyes suspect of angle closure or other angle pathology were excluded Ocular rigidity was tested and outflow facility values were corrected accordingly

The patients were divided into 3 dosage and duration of treatment groups as used by Blake et al (1950) and Bernstein & Schwartz (1962) (Table I) The minimum daily dose was 20 mg Meticorten

Twenty eight patients were males and 32 females (Table II) and the mean age was 49 years Table III shows the systemic disease for which the patients were treated with systemic steroids

The mean values obtained for intraocular pressure outflow facility and logarithm of the Po/c ratio before and after water drinking were compared with mean values from a screened outpatient group of healthy subjects with clinically normal eyes and a negative personal and familial glaucoma history They were matched with the steroid group for age and sex In both these groups the steroid group and the control group only one eye the right eye was tested In the control group investigated for another purpose a water drinking test had not been performed and analogous values quoted in the literature (Levene 1961 Becker 1961) were used for comparison as cited by Bernstein & Schwartz (1962) We assumed that our statistical analysis is unaffected by sampling errors since in the steroid group there was no evidence of an overt or suspect glaucoma and no family history of this disease The ideal control group of patients suffering from identical systemic disease but not treated with systemic steroids was not available

Contrary to the innumerable efforts to elucidate and to define the ocular hypertensive response to topically applied steroids investigations of the effect of systemic steroids have remained relatively scarce They are limited to a smaller number of investigations the largest comprising 48 cases (Bernstein & Schwartz 1962) This discrepancy might be due to the fact that most of these patients were not primarily ophthalmological cases and the virtually symptomless nature of the ocular hypertensive phenomenon did not attract the attention of the attending physicians On the other hand ophthalmological cases treated with systemic steroids are usually an unsuitable material to differentiate between the effect of systemic steroids on ocular fluid dynamics and that of the basic disorder Nor is there any unanimity in the results of the various investigators (Bernstein & Schwartz 1962 Blake et al 1950 Kern 1967) apparently due to the lack of a clearly defined ocular response to systemically administered steroids Goldmann (1966) found in a critical survey of the literature only four cases which fulfil all the requirements of a clear proof of at least transitory ocular hypertension due to systemic steroids These gaps in knowledge led us to reinvestigate some of the inherent problems on a broader basis This report deals with the distribution of the magnitude of the ocular response in a systemic steroid treated population and its dependence on dosage and duration of the treatment

Material and Methods

The study included 60 patients treated in various departments of our hospital and other hospitals of the Tel Aviv area for different diseases with long term systemic steroids of varying dosages and durations Patients with previous

Table I

Classification of patients as to duration and dosage of therapy with systemic steroids

Duration	Dose of meticorten (mg/day)			
	20	30	40 or more	Total
< 1 year	5	8	4	17
1–4 years	12	6	3	21
> 4 years	17	2	3	22
Total	34	16	10	60

Table II
Age and sex of patients in the steroid series

Age	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Total
Males	1	2	6	4	4	6	3	2	28
Females		5	3	4	7	4	8	1	32
Total	1	7	9	8	11	10	11	3	60

ocular diseases or surgery or suffering from secondary glaucoma were excluded from this study

Each patient was submitted to a complete eye examination including biomicroscopy and perimetry Intraocular pressure was measured by applanation and tonography was done before and after water drinking Only technically perfect tonograms were evaluated All cases with eyes suspect of angle closure or other angle pathology were excluded Ocular rigidity was tested and outflow facility values were corrected accordingly

The patients were divided into 3 dosage and duration of treatment groups as used by Blake et al (1950) and Bernstein & Schwartz (1962) (Table I) The minimum daily dose was 20 mg Meticorten

Twenty eight patients were males and 32 females (Table II) and the mean age was 42 years Table III shows the systemic disease for which the patients were treated with systemic steroids

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Table III
Systemic diseases of steroid treated patients

Collagen disease		9
Lupus erythematosus	6	
Dermatomyositis	3	
Blood disease		18
Hemolytic anemia	7	
Acute leukemia	2	
Chronic leukemia	8	
Thrombopenia	1	
Rheumatic arthritis		6
Asthma		8
Pemphigus		14
Ulcerative colitis		4
Nephrotic syndrome		1
	Total	60

The data were evaluated statistically using the Z test for differences between means In the intergroup analysis of the steroid patients the F test was applied for significance differences and to demonstrate the necessary difference the least significant difference test was employed The level of significance chosen was 5 % ($P \leq 0\ 05$) for all tests

Results and Discussion

Table IV summarizes the results of the investigation On comparing the means of the steroid group to the means of our normal group and/or the literature populations significant differences were found for applanation pressure ($P < 0\ 001$) for the logarithm Po/C before water drinking ($P < 0\ 01$) in comparison with our normal group and for the logarithm Po/C after water drinking ($P = 0\ 005$) compared to the value of the literature population However no significant difference was found for the other parameters with the exception of the values of outflow facility after water load where the difference approached the level of significance ($P = 0\ 053$) Calculation of the difference between outflow pressures of the steroid and the control group showed that the

Table IV

Data of steroid group compared to our normal control group and literature populations

	Steroid group	Control group	Literature population
Applanation pressure (mmHg)	17 73 ±3 38 (60)	16 00 ±2 19 (60)	15 60 ±3 35 (979)
Outflow facility before water (μl/min/mmHg)	0 307±0 083 (60)	0 31?±0 037 (60)	
Outflow facility after water (μl/min/mmHg)	0 261±0 078 (50)		0 280±0 0₅ (909)
Log Po/C before water	1 769±0 176 (60)	1 730±0 140 (60)	
Log Po/C after water	1 833±0 193 (50)		1 7₀0±0 130 (909)

Mean±standard deviation (No eyes)

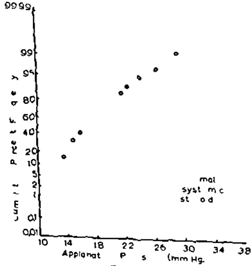


Fig 1

Probability plot of frequency distribution of applanation pressures

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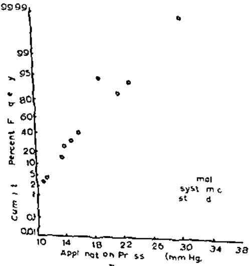


Fig 1

Probability plot of frequency distribution of applanation pressures

Table I
Per cent frequency of applanation pressures (mmHg) in patients treated with systemic steroids

Author year	No of patients	Average dose of prednisone (mg/day)	Pressure (%)		
			< 20	20–31	> 31
Lee (1958)	13	18	54	46	0
Bernstein & Schwartz (1962)	48	16	76	24	0
Howland & Ellis (1967)	26	24	69	29	2
Godel Feiler Ofry & Stein (1972)	60	30*	67	33	0

* Meticorten (mg/day)

mean outflow pressure in the steroid group was 25 % and 34 % higher than that of our normal group and the literature population respectively

In contrast to the findings of Bernstein & Schwartz (1962) no significant difference was noted for ocular rigidity in our sample between the steroid group and the normal group The mean ocular rigidity in our steroid group was 0 0224 and the standard deviation ± 0 0085 Only 4 patients had a low scleral rigidity ranging from 0 014 to 0 0185

To detect whether the differences in means of the various parameters were due to the influence of the drug on all subjects of the sample or only on a certain number of individuals cumulative per cent frequency plots were drawn Fig 1 shows the plot for the applanation pressures of the steroid treated and our normal group While the normal group exhibited an approximately normal distribution the steroid group displayed a marked deviation from a straight line in the upper end of the curve the starting point of the deviation situated at about 60 % This skewed distribution in the upper end of the curve may be considered as evidence of the presence within the sample of individuals who responded to systemic steroids in a different way than the rest of the sample

About 34 % of the patients on systemic steroids had applanation pressures of 20 mmHg or more while only 6 % of the normal control group fell into this category Table V shows that the per cent frequency distribution of applanation pressures as exhibited by our steroid patients is in good agreement with that found by other authors

Probability plots of the frequency distribution of outflow facility values before water drinking did not show any obvious deviation from that of the normal group Only after water provocative tonography could a minor deviation from linearity be seen in the lower values of C below 0 18 μl/min/mmHg The same frequency distribution tests were applied in the evaluation of the logarithm of the Po/c ratio Only the values after water load exhibited a skewing in the bar graph and deviation in the cumulative per cent frequency plot This deviation was however not so marked as in the plots of applanation pressures In the interests of saving space these graphs and plots have been omitted

Since a highly significant difference was found for the mean ocular pressure between the steroid and normal group but the means of the tonographic C values were not significantly different one has to assume that the mechanism of the higher pressures in patients treated with systemic steroids must include an increase in the rate of formation of aqueous humor (F) This assumption is somewhat at variance with what is generally found with topically applied steroids We tested therefore the F values – using the formula F = C (Po – 10) despite its well known weakness – first for the whole groups and then for the subgroups of patients with pressures of 20 mmHg or more occupying the upper end of the cumulative per cent frequency plot In the first instance no significant difference of the F values between the steroid and normal group was disclosed but in the second instance the F values were significantly higher

Table VI
Effect of steroid dosage

	Meticorten (mg/day)		
	20	30	40 or more
Applanation pressure (mmHg)	16 79 ±2 71 (34)	18 37 ±3 36 (16)	19 90 ±4 45 (10)
Outflow facility before water (μl min mmHg)	0 3[illegible]0±0 070 (34)	0 250±0 060 (16)	0 [illegible]90±0 110 (10)
Outflow facility after water (μl min mmHg)	0 [illegible]0±0 0[illegible]0 (29)	0 240±0 070 (1[illegible])	0 [illegible]50±0 050 (9)
Log Po/C before water	1 730±0 155 (34)	1 908±0 158 (16)	1 841±0 244 (10)
Log Po/C after water	1 8[illegible]4±0 167 (29)	1 962±0 198 (12)	1 956±0 216 (9)

Mean ± standard deviation (No eyes)

Table VII
Effect of duration of treatment*

	1 year	1–4 years	4 years
Applanation pressure (mmHg)	19.17 ±4.40 (17)	17.52 ±3.26 (21)	16.81 ±2.15 (22)
Outflow facility before water (μl/min/mmHg)	0.302±0.099 (17)	0.328±0.076 (21)	0.290±0.071 (22)
Outflow facility after water (μl/min/mmHg)	0.246±0.094 (12)	0.238±0.079 (19)	0.247±0.064 (19)
Log Po/C before water	1.819±0.222 (17)	1.730±0.169 (21)	1.769±0.137 (22)
Log Po/C after water	1.966±0.264 (12)	1.838±0.182 (19)	1.876±0.139 (19)

* Mean±standard deviation (No eyes)

($P < 0.01$) It seems therefore that the higher intraocular pressures in the steroid group could not be attributed to a reduction in outflow facility but are due to an increased formation of aqueous humor This distinction between the effect of systemically and topically administered steroids was observed also by others (Linnér 1959 Draeger 1965 Patterson & Owen 1966) and was associated with the different routes of entrance of the drug into the eye which might evoke different changes in ocular fluid dynamics

Bernstein & Schwartz (1962) reported significantly higher means of applanation pressure in patients who had received systemic steroids for longer than four years in comparison to those who were treated for less than one year This claim of the influence of the time factor was then taken for granted by other authors (Goldmann 1966 Schwartz 1966) We thus analyzed in a similar way the statistical results of the influence of dose and duration (Tables VI and VII) Significant differences were disclosed in the mean applanation pressure The higher the dose the higher the mean pressure especially when the low dosage group was compared to the high dosage group On the other hand an apparently paradoxical result in contrast to the claim of Bernstein & Schwartz was obtained in the statistical analysis of the duration of therapy group The mean of the applanation pressures of patients treated for less than one year was significantly higher than that of those treated for four years or longer Further investigation of this apparent paradox disclosed that in our short term treated group of 17 patients, 7 were treated with moderate and 6 with high doses of the drug while in the group of patients who had treatment for 4 years or

longer 70 % were treated with low doses since an initially high dosage had been in many patients in the lapse of time gradually reduced for various reasons Thus from the result of our investigation it would seem that it is not the duration of therapy but rather the dosage which is the deciding factor In a second report we will show that provided a minimum dose and duration of treatment are given the determinant of the hypertensive response is the reaction of the individual patient to steroids and not the dosage or the duration of treatment Discrepancies in results of different authors are due to different composition of samples

No significant differences between the means of the different disease groups were detected for the various measurements

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SYSTEMIC STEROIDS AND OCULAR FLUID DYNAMICS II

Systemic Versus Topical Steroids

BY

V GODEL V FEILER OFRY and R STEIN

In 59 patients treated with long term systemic steroids 3 distinct groups with different levels of sensitivity to the steroid effect on intraocular pressure and fluid dynamics could be distinguished by a topical dexamethasone test The percental distribution of the 3 pressure rise level groups and the mean pressure change within each group were equal to those found in a normal population not pre treated with systemic steroids Whereas only 16 % of the patients with steroid pressures lower than 18 mmHg were sensitive to topically applied dexamethasone 70 % of the patients responding with intermediate and high pressure rise to topical dexamethasone had systemic steroid pressures in the range of 18 mmHg or more The effect of systemic steroids on ocular pressure apparently does not affect the magnitude of pressure elevation induced in the positive responders by topical dexamethasone
Intergroup analysis of the steroid group classified according to dosage and duration of treatment proved that differences in mean values of ap planation pressure between the subgroups depend solely on the proportion of positive and negative steroid responders within the subgroups
The mean systemic steroid C value in the group of patients responding to topical steroid with pressure elevation of 6 mmHg or more was only 10 % lower than the same value in patients regarded as non responders by the

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topical dexamethasone test While pressures of 20 mmHg or more in systemic steroid patients are strongly suspected to be due to the steroid eff ct systemic stero d C values lack such predictive value In accordance with Armaly it was found that the magnitude of the red ction in outflow f cility after topically applied dexamethasone wa directly related to the initial C and irrespective of this valu wa greater by a constant and equal amount in steroid responders than in non responders It was sim larly found that while in non responders the per cent reduction in C values after topical dexamethasone increased with the initial C value in responders the reduction remained fairly constant and independent of the original C value It amounted in our steroid patients to almost the same va' e (50°) as in Armaly s group of normal volunteers The rate of for mation of aqueous humor effected by systemic steroids was higher in patients classified as responders according to the effect of topical steroids on the pressure or the outflow facility This fact is evidence that system c steroids exert their influence on ocular pressure in sensitive individuals mainly by an increased inflow

Key words intraocular tension – aqueous dynamics – steroids

An investigation of patients treated with long term systemic steroids showed that some of the parameters characterizing ocular fluid dynamics differed sig nificantly from those in a normal control group The most striking difference was found for the mean applanation pressure while no difference or only an insignificant one could be detected for the mean outflow facility coefficient before and after water provocative tests Plots of the cumulative frequency distribution of the applanation pressures in the steroid treated patients dis played a marked shift to the right at the upper end of the curve In this part of the curve 34 % of the patients with pressures of 20 mmHg or more were represented It seemed therefore that it was mainly this proportion of patients which was responsible for the higher mean applanation pressure of the steroid group As the ocular fluid dynamics before systemic steroid therapy was not known except for 2 patients (Godel Feiler Ofry & Stein 1970) information was lacking as to how many of the patients represented at the tail end of the cumulative per cent frequency plot were in this location due to the influence of the systemic steroids on the ocular pressure and whether those represented in the lower portion of the plot were refractory that is non or low responders to steroids As it is known that the response of ocular pressure to topical steroids appears to be differential it was decided to subject all the patients to a topical dexamethasone provo ative test in order to clarify these questions

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Intergroup analysis of the steroid group classified according to dosage and duration of treatment proved that differences in mean values of applanation pressure between the subgroups depend solely on the proportion of positive and negative steroid responders within the subgroups

The mean systemic steroid C value in the group of patients responding to topical steroid with pressure elevation of 6 mmHg or more was only 10 % lower than the same value in patients regarded as non responders by the

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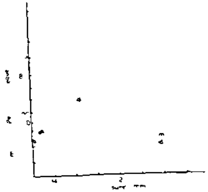


Fig 1
Frequency distribution of applanation pressures of 59 patients on systemic steroids before (circles) and after 4 weeks of topical dexamethasone in the right eye (triangles)

before and after topical steroids showed that topical dexamethasone elicited a further deviation of the upper end of the curve when compared to the deviation effected by systemic steroids (Fig 1) In order to detect the relationship between the response to systemic and topical steroids the pressure before instillation of dexamethasone in the right eye of each patient (abscissa) was plotted against the pressure change following the dexamethasone provocative test (ordinate) (Fig 2) Three distinct groups became discernible each exhibiting a different magnitude of pressure elevation Group I with pressure rises up to 5 mmHg consisted of 39 patients or 66 1 % of the sample with a mean pressure elevation of 1 8 mmHg and a standard deviation of 2 2 mmHg The patients of this group were regarded as non or low responders Group II was subdivided into Group IIa and Group IIb according to the magnitude of the pressure increase Group IIa with an intermediate pressure elevation of 6 to 15 mmHg included 18 patients or 30 5 % of the sample with a mean pressure increase of 9 8 mmHg and a standard deviation of 1 9 mmHg Group IIb with a high level response of 16 mmHg or more included only 2 patients or 3 3 % of the sample with pressure rises of 22 and 24 mmHg respectively Comparing these figures with those of Armaly (1966a) which he considered to be typical of the distribution of the different levels of the hypertensive ocular response to topical steroids in a normal population one is surprised by the almost complete similarity of the data One would have expected that eyes with pressure eleva

Material and Methods

The patients who were examined in the investigation reported in Part I of this study (Godel Feiler Ofry & Stein 1972) were recruited once again and instructed to instill 0 1 % dexamethasone drops in their right eye 3 times daily for 4 weeks Their co operation was satisfactory and only one refused and was thus excluded Applanation pressures were recorded weekly and tonography was performed at the beginning of the experiment and after 4 weeks

Results and Discussion

THE EFFECT OF TOPICAL DEXAMETHASONE ON OCULAR PRESSURE IN PATIENTS ON LONG TERM SYSTEMIC STEROIDS

From Table I it is evident that dexamethasone applied topically for 4 weeks caused a significant increase in the mean applanation pressure in addition to the elevation which was already present due to the effect of the systemically administered steroids The mean ocular pressure of the whole sample rose by 26 % The cumulative per cent frequency distribution curves of the pressures

Table I

Effect of topical dexamethasone on applanation pressure in 59 patients treated with systemic steroids

	Before	After
	Topical dexamethasone	
Applanation pressure (mmHg)	17 78 ± 3 38●	22 50 ± 4 44●
ΔP	4 96 ± 5 26	
P_{A1}/P_{A0}	1 26 ± 0 26	

ΔP Change in applanation pressure after 4 weeks of topical dexamethasone (mean ± standard deviation)

P_{A1} Applanation pressure after 4 weeks of topical dexamethasone P_{A0} applanation pressure before dexamethasone

● Difference significant at $P < 0\ 001$

Table II

Applanation pressure in the two pressure rise level groups I and II and the effect of topical dexamethasone in 59 patients on systemic steroids

Mean applanation pressure (mmHg) ± S D	Group I n = 39	Group II n = 20
Before dexamethasone	16.3 ± 2.4●	20.7 ± 3.1●
After 4 week of dexamethasone	18.3 ± 2.9	31.6 ± 5.6●

Group I Patients with pressure rises up to 5 mmHg after 4 weeks of topical dexamethasone

Group II Patients with pressure rises of 6 mmHg or more after 4 weeks of topical dexamethasone

● Difference significant at $P < 0.001$

by the dexamethasone provocative test In contrast only 26 % of the positive steroid responders were present in the low dosage group and 10 % in the long duration group It is therefore the random proportion of positive and negative steroid responders both within the whole sample and within its intergroups that determines differences in mean values

Eight patients belonging to Group I and 5 to Group IIa were instructed after 4 weeks of topical application of dexamethasone to *continue drops for* an additional 3 weeks None of the cases in Group I showed a *further increase* in pressure and in 3 cases the pressure even dropped by 1 to 3 mmHg On the other hand in the 5 cases selected from Group IIa the pressure continued to rise and in two of them the pressure rose above the *limiting level* defined between Group IIa and IIb This qualitative *difference in the* behaviour of the ocular pressure between the two major *groups is apparently* not characteristic of systemically administered steroids Only *one of the 20* steroid responders had a pressure of 29 mmHg under the influence of systemic steroids and one of ?? mmHg while in all the others the *pressure* was in the range of 15 to 22 mmHg and this despite treatment with high and *moderate* doses of meticorten for over 4 years in ? cases and 1 to 3 years in *8 cases* It may be also noted that none of the steroid responders of our sample presented changes of the optic disc or visual field defects

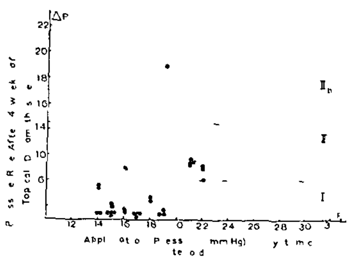


Fig 2

Correlation diagrams of change in applanation pressure after 4 weeks of topical dexamethasone in the right eye (ordinate) and the initial systemic steroid pressure (abcissa) Group I Patients with pressure rises up to 6 mmHg Group IIa Patients with pressure rises of 6 to 15 mmHg Group IIb Patients with pressure rises of more than 15 mmHg

tions already present due to the effect of systemic steroids should have responded to an additional treatment of topical steroids with proportionately lower pressure rises Since this was not the case and the proportion of intermediate and high responders as well as the magnitude of the response to topical dexamethasone was the same as in a sample not pre treated with systemic steroids one has to assume that the two different routes of administration of the drug produce pressure changes at least partly by different mechanisms

Table II shows that the mean applanation pressure in Group II (IIa + IIb) was about 27 % higher than in Group I and that this difference rose to about 68 % after treatment with topical steroids

Intergroup analysis of the steroid patients according to dosage and duration of treatment (Godel et al 1972) showed significantly higher mean applanation pressures for the high dosage group and paradoxically also for the short duration group This is in contrast to the statement of Bernstein & Schwartz (1962) who noted a significantly higher mean applanation pressure in patients who received steroids for longer than 4 years in comparison to those being treated for less than one year Investigation of the different dosage and duration of therapy groups of our sample revealed that in the high dosage group of 10 patients and in the short duration group of 17 patients about 60 % of the individuals belonged to the intermediate or high level response groups as proved

Table III

Chan e in outflow facility (C) in the two groups of different magnitude of pressure rise after topical dexamethasone

	No of patients	C (μl/min/mmHg) Mean ± S D	r
Group I	[illegible]9		
$C_{0\ \ k}$		0 3[illegible]3 ± 0 07[illegible]	0 62
$C_{0\ we\ k}-C_{4\ w\ \ k}$		−0 081 ± 0 070	
Group II*	[illegible]0		
$C_{0\ week}$		0 [illegible]90 ± 0 093	0 75
$C_{0\ w\ \ k}-C_{4\ weeks}$		−0 130 ± 0 069	

Group I Patients with pressure rises of less than 6 mmHg

Group II Patients with pressure rises of 6 mmHg or more after 4 weeks of topical *dexamethasone*

r Coefficient of correlation

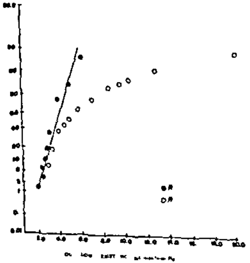


Fig 3

F equency distribut n of outflow res stance values in 59 pat ents on *systemic steroids* *b f re* (sol d circles) and *after 4* weeks of topical dexamethasone in the right eye (open circles)

V Codel P Feiler Ofry and R Stein

EFFECT OF TOPICAL DEXAMETHASONE ON OUTFLOW FACILITY IN PATIENTS ON SYSTEMIC STEROIDS

There is considerable evidence of the heterogeneity of response to steroids as far as steroid induced ocular hypertension is concerned and of the presence of at least two populations with not only quantitative but also qualitative distinct characteristics but results of investigations of the influence of steroids on out flow facility have been inconsistent Generally a decrease in outflow facility related to an increase in pressure has been found after topical application of steroids (Armaly 1965 1966a Becker 1965) Several observers (Linnér 1959 Nicholas 1964 Draeger 1965) however have noted that in a significant pro portion of individuals an adequate reduction in outflow facility was not shown

In order to analyse the behaviour of our group in this respect the sample was divided into 2 groups according to the level of pressure rise following topical dexamethasone Group I comprised 39 patients who responded to dexa methasone with a pressure rise up to 5 mmHg and Group II the remaining 20 patients with pressure elevations of 6 mmHg or more Comparing the mean C values before topical dexamethasone to the mean C of our normal control group quoted in Part I of this study ($C = 0.312 \pm 0.087$) one finds that there was no obvious effect of the systemic steroids on outflow facility

Table III shows a small difference of mean outflow facility between the two groups However after 4 weeks of topical dexamethasone a significant dif ference was found

An arrangement of the resistance of outflow values of the whole steroid group in a cumulative per cent frequency plot (Fig 3) – resistance being chosen instead of facility because it produces a clearer picture – revealed that the resistance values even though under the influence of systemic steroids described a single distribution indicating thus the failure of systemic steroids to exert the expected differential influence on outflow resistance Treatment with topical dexamethasone however produced a marked deviation of the curve from a linear representative The first deviation occurred at a point of about 30 % and this part included all patients with outflow resistance up to 4 (μl/min/mmHg) $^{-1}$ and the second at a point of about 90 % separating the pa tients with a resistance higher than 8 (μl/min/mmHg) $^{-1}$

Then we investigated whether there is a relationship between the 3 groups representing the different levels of pressure rise and the differential decrease in outflow facility after topical dexamethasone and its dependence on the starting systemic steroid outflow values

The sample was divided into 3 groups (A B and C) according to the per cental reduction of outflow facility following topical dexamethasone In Table

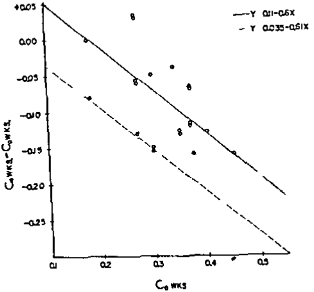


Fig 4

Correlation diagram and regression l ne of the change in mean outflow facility in the right eye after 4 weeks of topical dexamethasone (ord nate $C_{4\,wk}-C_{0\,wk}$) and the initial systemic steroid C value (abscissa $C_{0\,wk}$) in 59 patients on systemic steroids Data of Group I in open circles and solid l ne and of Group II in solid circles and interrupted line

in an attempt to evaluate qualitative differences in the behaviour of outflow facility between the two groups of different level of pressure rise following treatment with topical steroids We were interested in determining whether Armaly s intriguing findings in 80 subjects with clinically normal eyes treated with dexamethasone have general validity and analysed our sample of 59 patients who were on systemic steroids Fig 4 demonstrates the correlation between the change in outflow facility (C) and the initial C values and Fig 5 illustrates the correlation between the per cent reduction in C after topical dexamethasone and the initial C for the two Groups I and II

Comparing the findings of Armaly with those of our sample one is sur prised by the similarity of the results despite the fact that our patients were treated with systemic steroids A significant positive correlation between the magnitude of the change in C and the initial C value was present in the two groups of both samples The parallelism of the slope of the regression lines expressed for Group I by the equation $Y = 0.11 - 0.60X$ and for Group II by the equation $Y = 0.035 - 0.61X$ shows that independent of the initial C

Table II

Reduction of outflow facility after topical dexamethasone in 59 patients on systemic steroids

Group	Outflow facility reduction			
	A	B	C	Total
	< 40 %	40–60 %	> 60 %	
C●	0.30 ± 0.07	0.29 ± 0.14	0.29 ± 0.09	
ΔC●●	0.09 ± 0.04	0.14 ± 0.08	0.23 ± 0.08	
No of patients	35	15	9	59

C● Mean ± standard deviation of outflow facility before topical dexamethasone but under the influence of systemic steroids

ΔC●● Mean ± standard deviation of reduction in outflow facility after 4 weeks of topical dexamethasone

IV Group A represents all patients with an outflow facility reduction up to 40 % It comprises 35 patients or 60 % of the sample with a decrease in outflow facility of 0.09 ± 0.04 μl/min/mmHg Group B with a reduction of C of 40 to 60 % corresponding to a mean reduction of 0.14 ± 0.08 μl/min/mmHg was represented by 15 patients or 25 % of the sample Group C with a reduction of outflow facility of more than 60 % was composed of 9 patients or 15 % of the sample the reduction of C amounted to 0.25 ± 0.08 μl/min/mmHg

Analyzing the sample we could not find a correlation between the 3 groups of outflow reduction and the 3 pressure rise level groups Similar discrepancies between the decrease in outflow facility and an adequate increase in pressure or vice versa were noted also by others (Armaly 1966b) Since intraocular pressure is dependent both on aqueous formation and on resistance to outflow through conventional and unconventional channels of drainage and each of these factors may be affected in a different way and degree by systemic and topical steroids a homogeneous change might be rather an exception The systemic steroid C values therefore do not indicate whether an individual treated with systemic steroids belongs to a negative or a positive steroid responder group

Armaly (1966b 1967) examined the correlation both between the change in C ($C_{4\,weeks} - C_{0\,week}$) and the per cent reduction in facility $\frac{C_{4\,weeks} \times 100}{C_{0\,week}}$

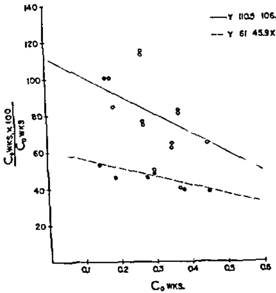


Fig 3

Correlation diagram and regressive lines of the percentage change in C values after 4 weeks of topical dexamethasone ($\frac{C_{4\ week} \times 100}{C_{0\ week}}$ ordinate) and the initial systemic steroid C values ($C_{0\ week}$ abscissa) in group I (open circles and solid line) and in Group II (solid circles and interrupted line)

nating these two values our regression line became identical with that of Armaly and intersected the ordinate at about 48 % thus indicating that in Group II the per cent reduction is independent of the initial C value Comparing the findings of our steroid group to those of Armaly s normal group one has to conclude that the pre treatment with systemic steroids did not change the qualitative differences in behaviour of the outflow facility in response to topical steroids

Finally we examined the rate of formation of aqueous humor (F) for the whole steroid group and separately for its subgroups I and II as well as for the subgroups A B and C which were defined by the magnitude of change in applanation pressure and outflow facility respectively after topical treatment with dexamethasone Table V shows that in spite of the reduction of outflow facility as documented in Tables III and IV the F values in Groups B and C before dexamethasone drops are significantly higher than in the other subgroups The F values in subgroup B were less characteristic since this

Table I
Mean rate of aqueous humor formation (F) in 59 patients on systemic steroids before and after topical dexamethasone

	No of patients	F (μl/min) Topical dexamethasone	
		Before	After
Whole group	59	2 30±0 97	2 21±0 55
Group*	39	1 97±0 80	1 90±0 86
Group II**	20	2 74±1 04	2 85±1 04
Croup A●	35	1 99±0 75	2 20±0 48
Croup B●	15	2 63±0 87	2 24±1 24
Croup C●	9	2 93±1 20	2 20±0 48

* Group I Patients with pressure rises up to 6 mmHg after 4 weeks of topical dexamethasone

** *Group II Patients with pressure rises of 6 mmHg or more after 4 weeks of topical* dexamethasone

● Croup A Patients with a reduction of C of less than 40 %
Group B Patients with a reduction of C of 40 to 60 %
Group C Patients with a reduction of more than 60 % all after 4 weeks of topical dexamethasone

values the magnitude of the reduction in C due to the treatment with topical dexamethasone is constant for both groups being in Croup II greater by a constant value of about 0 075 μl/min/mmHg than in Croup I

While in Group I however not only the absolute but also the per cent reduction (Y = 110 6 – 106 2 X) were significantly correlated to the original C value no such correlation between the per cent reduction and the initial C value was found for Group II the steroid responders as documented by the regression line Y = 61 – 59 X The reduction in Group II ranged from 56 to 38 % (47±6 7 %) and the *regression line is significantly different from* one parallel to the abscissa as it was in Armaly s sample This difference may be due to the small sample or to the effect of the extreme values of the change of C in two cases the accuracy of which we were not able to recheck I him

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STUDIES ON THE OCULAR PULSE PRESSURE WAVE IN HUMAN DOG AND RABBIT EYES WITH A PNEUMATIC TONOMETER

BY

ASBJØRN M TØNJUM

A method of studying the intraocular pressure and the ocular pulse pressure by means of pneumatic tonometry is described Reproducible recordings have been obtained even in conscious rabbits and dogs The reliability of the recordings of the ocular pulse pressure or the ocular pulse wave amplitudes has been confirmed by comparison with a manometric system in which particular attention was paid to the design to avoid damping of the pulse wave There was fairly good agreement between the values of the pulse pressures obtained with these two methods Values of intraocular pressures and ocular pulse pressures recorded with the pneumatic tonometer in normal human rabbit and dog eyes are given The ocular pulse pressure values found were considerably higher than those reported by investigators using other methods and other experimental conditions

Key words ocular pulse pressure – pneumatic tonometry – conscious animal

Pulsations of the eye have been known for more than one hundred years Detailed studies of the ocular pulsations were done by Thiel (1928) who devised an apparatus to record the reflection of a light beam from a mirror resting on the cornea Since then a variety of methods have been employed to

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subgroup was composed of equal numbers of responders and non responders as far as pressure rises were concerned From this it has to be concluded that provided that the patient belongs to the group of steroid responders the increases in pressure following systemically administered steroids are due mainly to an increased formation of aqueous humor On the other hand topical steroids failed to elicit a significant change of the F values that might conceivably account for the increases in pressure

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pneumatic tonometry recordings were done during general anesthesia with Fluothane This eye was to be enucleated from a 34 year old female patient because of a small intrabulbar malignant melanoma

The rabbits were 30 New Zealand albinos weighing 2–3 kg

Six mongrel dogs with an average weight of 7.5 kg ranging from 6 to 8 6 kg had been reared in a kennel and were healthy

Methods

The recordings of the intraocular pressure and the ocular pulse pressure wave were done with the pneumatic tonometry device as described by Tønjum (1971) In this tonometric system the oxygen gas is supplied to the sensor at a gas pressure of 1 6 kg/cm or 20 lbs/in² The pressure in the gas chamber within the sensor was transmitted through a rigid polyethylene tubing (PE 190) to the pressure transducer Two recording systems have been used a) the one com bination was a Sanborn pressure transducer (267b) with Carrier preamplifier

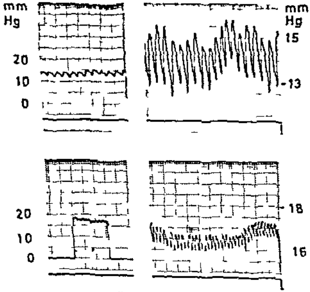


Fig 1

Pneumatic ton metry rec rdings of the intraocular pressure in a human and a rabbit ye (left) and of the ocular pulse pressure in a human and a rabbit eye (right)

study corneal pulsations (Susuki 1960 Bynke & Krakau 1964 Lester 1966) These methods have limitations in determining the exact size of the intraocular pressure variations Lawrence & Schlegel (1966) estimated the intraocular pulse pressure in generally anesthetized rabbits by means of manometry The term ocular pulse pressure (OPP) means here the difference between the intraocular pressure in systole and that in the diastole Bynke (1968) conducted similar experiments and included comparisons with his oculo sphygmographic instrument

van Beuningen (1960) described a refined electronic Schiotz tonometer and its application to the study of the intraocular pressure variations Since then a series of modifications in the design of this equipment have been described and their applications reported (Comberg & Pilz 1961 Davanger 1963 Krishna & Botelho 1963 Castrén & Lavikainen 1964 Rodriguez Barrios & Solis 1966 McLean & Galin 1966 Galin & Harris 1966 Bron Knox & Garsterland 1967 Horven 1968) Particular interest has been paid to the study of the changes of the intraocular pressure and the ocular pulsations in stenosis and occlusion of the carotid artery

However most methods influence the intraocular pressure and the blood circulation of the eye during the measurements Moreover examination with the electronic Schiotz tonometer is limited to the recumbent position vertical eye axis and cooperative subjects

Recently a new pneumatic tonometric device enabling a continuous recording of the intraocular pressure and its variations has been described (Tonjum 1971) This tonometer produces only a moderate increase of the intraocular pressure during the measurement To a large extent the measurement is independent of the direction of the eye axis and it is easy to use even on conscious animals

The purpose of this paper is to report the application of this device to the study of ocular pulse pressure waves and to present some comparative data on the intraocular pressure and the ocular pulse pressure in human rabbit and dog eyes

Material

The human subjects used were 20 healthy volunteers 7 females and 13 males Their average age was 36 years ranging from 15 to 72 years They have had no known ocular cerebral or circulatory disease and no refraction anomaly beyond 2 diopters They were not exceptionally physically fit None admitted to having recently used drugs which might have influenced the general blood circulation In one additional human eye comparison between manometric and

Manometric registrations were performed with the same recording equipment Sanborn as well as Statham transducers were used In order to avoid damping of the intraocular pressure variations in the manometric system rigid and straight 20 cm long nylon tubings (Portex) were interposed between the pressure transducer and the 19 gauge cannula which was gently pushed into the anterior chamber after a cut had been made almost through the cornea at the limbus with the point of a Graefe s knife

Simultaneous pneumatic tonometry and manometry were done in a human eye during general anesthesia with Fluothane The same procedures were per formed in 8 eyes belonging to the 6 dogs during general anesthesia with Nem butal Abbott (Pentobarbitone sodium) 35 mg per kg of body weight given slowly intravenously The lower eye lid of the dogs had to be removed in order to obtain access to the eye and to avoid pressure on the eye from the lids and the surrounding tissues

Results

A SIMULTANEOUS RECORDINGS OF THE OCULAR PULSE PRESSURE WAVES WITH MANOMETRY AND PNEUMATIC TONOMETRY

The manometric recording was done continuously and the pneumatic tonometer was applied intermittently This permitted us to compare the shape of the pulse waves and the magnitudes of the ocular pulse pressures recorded with these two methods and also to study the influence of the pneumatic tonometry upon the manometrically registered ocular pulse pressure

1 The shape of the pulse waves

The ocular pulse pressure waves had a similar shape as determined with mano metry and pneumatic tonometry which may be seen from Fig 3 The curves also attained their maxima and minima synchronously which was most easily seen from curves recorded at a high chart speed

2 The magnitudes of the ocular pulse pressures as recorded simultaneously with pneumatic tonometry and manometry

By comparing the ocular pulse pressures obtained with these two methods an attempt was made *to rule out whether* the ocular pulse pressure determined with pneumatic tonometry *represented the true* pulse pressure or whether it was damped or *amplified* The manometric scale readings were calculated into intraocular pressure (IOP) *in terms* of mmHg by comparison with the scale



Fig 2
Pneumatic tonometry of a conscious rabbit after topical anesthesia

(350–1100AS) activating a Sanborn two channel recorder (320) b) a Statham pressure transducer and a Beckman RS Dynograph recorder Both systems were supplied with zero suppression units and different chart speeds and gave reproducible recordings When measuring the intraocular pressure it was convenient to use a sensitivity setting which gave a needle deflection of about 1 mm/mmHg of intraocular pressure When studying the pulse waves the sensitivity was routinely increased 10 times but sometimes higher or lower sensitivities were required in order to achieve pulse amplitudes of a convenient size

The human subjects were examined with the pneumatic tonometer shortly after applanation tonometry (Goldmann) in the sitting position The cornea was anesthetized with two drops of 0 5 % proparacaine or 0 4 % oxibuprocaine

The conscious rabbits were given time to be acquainted with the experimental conditions and the measurements with the pneumatic tonometer were easily done with topical anesthesia without a box or a bag Their heads were gently supported while the animals sat on a table It was not necessary to restrict the movement of the eyelids The dogs were also examined while conscious in the sitting or the standing position not under the influence of drugs other than the topical anesthesia The eye lids were gently restricted but care was taken to avoid digital pressure against the orbital and the surrounding tissues The nictitating membrane did not interfere during the measurement

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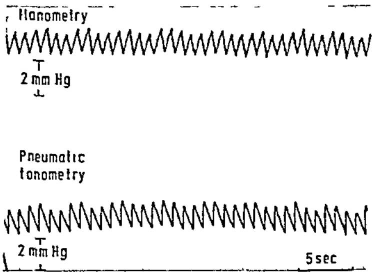


Fig 8
Simultaneous recordings of the ocular pulse pressure waves with manometry and pneumatic tonometry in a human eye with a small malignant melanoma during general anesthesia (curvilinear chart)

deflection obtained by stepwise elevation of a Ringer solution reservoir When only manometry was done this IOP was termed P When the pneumatic tonometer was applied the manometrically recorded IOP increased to P_{tp} i e the intraocular pressure during pneumatic tonometry The scale readings of the pneumatic tonometer represented both P and P_{tp} Therefore the scale readings had to be multiplied with one calibration factor in order to obtain the P value in mmHg and another one to obtain the P_{tp} value in mmHg The ocular pulse pressures (OPP) as recorded with manometry and with pneumatic tonometry as well were given in relation to the intraocular pressure level during pneumatic tonometry i e at P_{tp} In the human eye the difference between P_0 and P_{tp} was recorded to be 3 5 mmHg at P of 15 mmHg and 5 mmHg at P of 52 mmHg The average ocular pulse pressure of this eye in one specific period was 1 5 mmHg with manometry and 1 6 mmHg with pneumatic tonometry when P was 15 mmHg (see Fig 8) Manometry along with pneumatic tonometry was done successfully in the 8 dog eyes The average P of these eyes was 32 mmHg and the P_{tp} was 39 mmHg under the experimental conditions as described The paired readings of synchronous pulse waves revealed an average ocular pulse pressure of $2\ 41 \pm 1\ 28$ mmHg (± 1 SD) with manometry and $2\ 25 \pm 1\ 02$ mmHg with pneumatic tonometry

3 The influence of the pneumatic tonometry upon the manometrically determined ocular pulse pressure

Several experimental factors may influence the magnitude of the ocular pulse pressure during the measurement for instance the increase of the intraocular pressure the deformation of the eye and the possible changes of blood circulation through the eye caused by the measurement In the human eye a slight increase of the ocular pulse pressure at a P of 15 mmHg was recorded In the 8 dog eyes both slight increases and slight decreases in the magnitude of the pulsations were noticed after application of the pneumatic tonometer On an average there was a reduction of the OPP by 2 2 % ranging from an increase of 5 9 % to a decrease of 6 [illegible] % The changes did not exceed these limits even in 2 eyes with induced intraocular pressure of 50 mmHg It therefore seems reasonable to assume that the ocular pulse pressure determined with pneumatic tonometry closely approximates the amplitude size of the untouched eye

B INTRAOCULAR PRESSURE AND OCULAR PULSE PRESSURE (AT P_{10}) IN HUMAN SUBJECTS RABBITS AND DOGS DETERMINED WITH PNEUMATIC TONOMETRY

1 Normal human subjects

The intraocular pressure of the 20 human subjects in the sitting position was 14 4±1 9 mmHg in the right eyes and 14 5±2 3 mmHg in the left eyes The corresponding values recorded with a Goldmann applanation tonometer were 13 6±2 4 mmHg and 13 8±2 3 mmHg respectively Immediately after the pneumatic tonometry had been performed the ocular pulse pressure was recorded In the right eyes it was 2 9±0 9 mmHg ranging from 1 8 to 5 0 mmHg In the left eyes it was 2 9±0 9 mmHg ranging from 1 4 to 4 8 mmHg The heart rate was [illegible]3±10 beats per min the systolic blood pressure of the upper left arm was 128±18 mmHg and the diastolic blood pressure was 83±[illegible] mmHg

2 Conscious rabbits

The intraocular pressure was 19 6±2 4 mmHg of the right eyes and 18 9±2 6 mmHg of the left eyes The ocular pulse pressure was 0 8±0 3 mmHg of both eyes The ocular pulse pressure curves for the rabbits were steady as they were for the human subjects and it was fairly easy to determine the maxima and minima The average heart rate was 250 beats per minute ranging from 215 to [illegible]80 beats per min

3 Conscious dogs

The intraocular pressure of the right eyes was 24 [illegible]±4 8 mmHg and in the left eyes 24 4±4 9 mmHg The ocular pulse pressure was 1 [illegible]±0 2 mmHg in

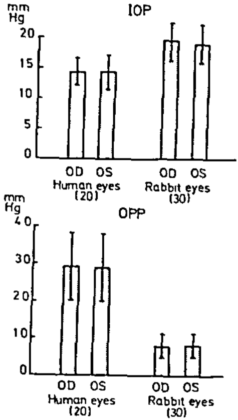


Fig 4

Intraocular pressure (IOP) and ocular pulse pressure (OPP) determined with pneumat
tonometry in 20 healthy volunteers and in 30 normal conscious rabbits

the right eyes and 1 8 ± 0 2 mmHg in the left eyes Their heart rate average
99 beats per min ranging from 65 to 140 beats per min The dogs used in th
series were adult but relatively small and the results therefore should no
be regarded as representative for the species Moreover the were restless an
more difficult to examine than the rabbits In addition the respiration had
considerable influence upon the magnitude of the ocular pulse pressure Becaus
of the relatively narrow interpalpebral fissures the digital pressure against th
palpebrae and the orbital tissues might induce errors into the measurements
This source of error was more easily avoided in the measurements of th
human and the rabbit eyes These difficulties however cannot alone explai
the relatively high intraocular pressures which were consistently recorded in
these dogs

Discussion

A routine method allowing reproducible continuous recordings of the intra ocular pressure and the ocular pulse pressure with a pneumatic tonometer has been described The calibration problems in measuring the intraocular pressure will be dealt with elsewhere (Tønjum 1972)

The shape of the recorded pulse waves and the magnitude of the ocular pulse pressure are dependent upon the rapidity and the accuracy with which the measuring devices react Comparison with manometric determinations makes it reasonable to assume that the ocular pulse pressure recorded with the pneumatic tonometer closely approximates the true pulse pressure during the measurement

A series of factors might influence the ocular pulse pressure during the measurement as compared with that in the untouched eye First the increase of the intraocular pressure from P to P_{tp} in most instances would influence the ocular pulse pressure by enlarging it Second the increased intraocular pressure might provoke a decrease of the blood circulation through the eye and thus reduce the ocular pulse pressure Third there is a deformation of the eye during the measurement which would tend to give a decrease Fourth a possible kinking of the orbital vessels might take place by displacement of the bulb during the measurement Bynke (1968) found a reduction of the manometrically recorded pulse amplitudes when loading the rabbit eye with his oculo sphygmo graphic instrument However in the present study little difference was found between the ocular pulse pressure *before* and *during* pneumatic tonometry as judged from the manometric registrations This may be related to the relatively little difference between the I and P_{tp} Therefore it is reasonable to assume that the size of the registered ocular pulse pressure is similar to that in the untouched eye

The magnitude of the ocular pulse pressure has been estimated previousl, by Davanger (1963) using an electronic Schoitz tonometer He found the ocular pulse pressure to be 0 9 mmHg ranging from 0 2 to 2 1 mmHg in a series of 37 patients with diagnosed os suspected glaucoma Horven (1970) found the average pulse pressure amplitudes with a similar method to be 1 39 mmHg in a series of 205 eyes with normal intraocular pressure mostly belonging to in patients of the Eye Department The existence of any abnormality or the use of any drug was not stated Lawrence & Schlegel (1966) estimated the ocular pulse pressure of rabbits in general anesthesia to be 0 9 mmHg by means of manometry For cannulation they used a 23 gauge needle connected with a PE 50 polyethylene tubing Bvnke (1968 1969) reported similar results from rab bits in general anesthesia

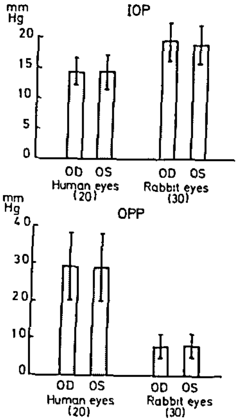


Fig 4

Intraocular pressure (IOP) and ocular pulse pressure (OPP) determined with pneumatic tonometry in 20 healthy volunteers and in 30 normal conscious rabbits

the right eyes and 1 8 ± 0 2 mmHg in the left eyes Their heart rate averaged 99 beats per min ranging from 65 to 140 beats per min The dogs used in this series were adult but relatively small and the results therefore should not be regarded as representative for the species Moreover they were restless and more difficult to examine than the rabbits In addition the respiration had a considerable influence upon the magnitude of the ocular pulse pressure Because of the relatively narrow interpalpebral fissures the digital pressure against the palpebrae and the orbital tissues might induce errors into the measurements This source of error was more easily avoided in the measurements of the human and the rabbit eyes These difficulties however cannot alone explain the relatively high intraocular pressures which were consistently recorded in these dogs

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The values for ocular pulse pressure in human and rabbit eyes in the present study therefore are 2–4 times larger than those estimated by previous investigators

It is not surprising that an electronic Schiotz tonometer would tend to give a damping of the intraocular pulse pressure wave because of the large increase of the intraocular pressure most probably accompanied by an influence upon the blood circulation through the eye a possible kinking of the intraorbital vessels and a considerable deformation of the eye during the measurement As shown by Bynke (1968) the application of his oculo sphygmographic instrument provoked a reduction of the amplitudes of the manometrically recorded pulse waves even though the weight of that instrument was less than that of the Schiotz tonometer The difference of the ocular pulse pressure obtained with the electronic Schiotz tonometer and the pneumatic tonometer might therefore to some extent be explained by basic methodological differences which ought to be examined more closely In the rabbit series of Lawrence & Schlegel (1966) the manometric set up may be assumed to give results similar to those of the present study A major difference exists however in their use of urethane general anesthesia which has a toxic effect upon the heart function and subsequently on the output for each heart beat which probably is a major determinant for the ocular pulse pressure Usually urethane also induces a considerable increase in the rate of the heart beats which in turn would tend to give a decrease of the cardiac output for each heart beat In some of the experiments *illustrated the rabbits seemed to have a heart rate of 350 beats per* minute some of which appeared to be premature In the present series of conscious undrugged rabbits of the same size the average heart rate was 250 beats per min In the rabbit series therefore the experimental conditions might to some extent explain the differences of the ocular pulse pressure values obtained with the pneumatic tonometer and other methods

The method described above might therefore be useful in the study of the intraocular pressure and the ocular pulse pressure as well in both human and animal eyes The recordings are reproducible and appear to be reliable as compared with simultaneous manometric recordings

Acknowledgment

I am indebted to Dr Robert Webb of the Block Engineering Inc Cambridge Mass for providing *the sensor of the pneumatic tonometer and valuable infor*mation Financial support from Anders Jahre s Fund for the Promotion of Science and from the Norwegian Research Council for Science and the Humanities is gratefully acknowledged

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CONGENITAL PIT OF THE OPTIC NERVE HEAD ASSOCIATED WITH SEROUS DETACHMENT OF THE MACULA

BY

EILA MUSTONEN and TOINI VARONEN

The biomicroscopic ophthalmoscopic and fluorescein angiographic features of macular detachment secondary to congenital pit of the optic nerve head in three patients are presented Fluorescein angiography failed to demonstrate evidence of dye leakage from choroidal retinal or optic nerve blood vessels into the subretinal fluid Diffuse fluorescence in the area of serous detachment, due to transmission of choroidal fluorescence through defects in the pigment epithelium was demonstrated in one patient All of these three patients were treated with photocoagulation along the temporal margin of the optic nerve head
A possible good result of this therapy is discussed

Key words optic pit – macular detachment – fluorescein angiography – photocoagulation

Congenital pits in the optic nerve are crater like holes or indentations in the surface of the optic disc They vary in location size depth and form The majority of congenital pits have been found in the lower temporal quadrant touching or nearly touching the edge of the disc The holes vary greatly in size generally being between $^1/_3$ and $^1/_8$ of the papilla diameter They are usually two to seven diopters in depth The majority of the pits are single as

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well as unilateral The pit itself is darker than the surrounding tissue and is usually round or oval the long axis being concentric with the disc margin The colour of the hole usually appears to be gray greenish or gray white Occasionally blood vessels emerge from the pit Frequently glial tissue is observed in the cavity and it can be difficult to estimate the depth of the pit

Since the first description of a congenital pit of the optic disc (Wiethe 1882) many cases have been reported Greear (1942) published a collective review of 69 previously reported cases of a crater like hole in the optic disc and described three of his own cases In Scandinavian literature also pits in the optic disc have been reported Nielsen (1924) described one case and Edmund (1930) reported two cases from Denmark Fisum (1957) added two cases from Denmark to the previously published world total of 80 cases From Norway Petersen (1958) reported 9 cases of pits in the optic disc Of these patients three had a temporary macular oedema with metamorphosia and reduced vision Gjessing (1959) described one case of a crater like hole in the optic disc

Kranenburg (1960) reported 24 cases of pits in the optic disc and reviewed the world literature from which he gathered descriptions of 123 cases These 147 cases comprise the largest and most important material The incidence of congenital pits of the optic nerve has been estimated as 1 11 000 patients with ocular complaints by Kranenburg who found 46 per cent to be located tem poro inferiorly He analysed the visual fields and found defects in 50 per cent of the 95 cases with fields described Of his own cases 16 showed central scotomas but all 24 showed enlarged blind spots or arcuate scotomas He re ported a characteristic picture of central serous retinopathy in at least 30 per cent and a post retinopathic state in another 20 per cent of his cases He explains the macular lesions as a defensive tissue response in the macular region which because of papillomacular bundle involvement has lower re sistance to seemingly slight noxious agents Sugar (1962) described 6 cases of pits in the optic disc and considered the macular lesion a more mechanically produced condition probably due to an actual leak of aqueous from the vit reous chamber through the pit into the subretinal spaces Sugar (1964 1967) wrote further on the subject giving this mechanical explanation for the as sociated macular pathology Regenbogen Stein & Lazar (1964) mentioned the possibility that the retinal detachment is due to a communication between the cavity of the pit and the adjacent subarachnoidal space through which fluid may seep under the retina

Johnson Smith & Hart (1963) reported the first case of macular lesion with congenital pit of the optic disc studied by the technique of intravenous fluor escein fundus photography Cass (1969) presented ophthalmoscopic biomicro

copic and fluorescein angiographic features of macular detachment secondary o congenital pit of the optic nerve head in five patients Angiography failed o demonstrate evidence of dye leakage from choroidal retinal or optic nerve blood vessels into the subretinal fluid Evidence was presented that the sub etinal fluid may be cerebrospinal fluid or vitreous humour entering the sub etinal space via the optic pit Photocoagulation along the temporal margin of the optic nerve head failed to re attach the macula Gordon & Chatfield (1969) reported 1[9] cases of pits in the optic disc Eight had macular pathology Fluorescein angiography showed two different pirtures Features of a detach nent of the retinal pigment epithelium were revealed in one case In another case the oedema was in the neurosensory retina and did not extend deep enou h to reach the pigment epithelium There were no paramacular spots of dye leakage A bright glow of dye within the pit was seen in two cases It was suggested that the source of oedema is vessels with increased permeability within the pit and that fluid leaks out to track deep to the macula

We present three cases of serous detachment of the macula secondary to congenital pit of the optic nerve head treated with photocoagulation and followed up by fluorescein angiography and stereophotographs

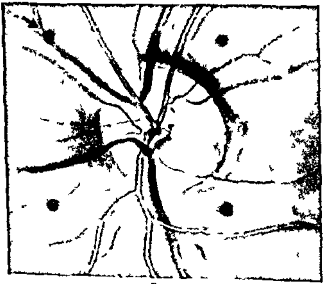


Fig 1

Ca e N 1 M K The left optic disc showed a tempo al crater like pit with small es ls emerg ng f om it The four dark dots (arrow) which are seen also in some th ph tographs are markings for stereogrammetric measurements not used in these pat ents

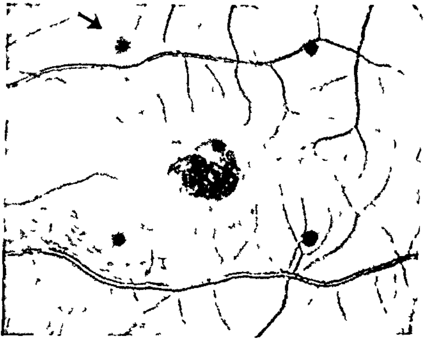


Fig 2
Case No 1 M K The left macula showed a circular detachment the size of a disc diameter with a macular hole



Fig 3
Case No 1 M K A slight choroidal fluorescence transmitted by pigment defects was seen in the macula

Case No 1

M K a 13 year old boy had been examined in school two years earlier at which time his visual acuity was reported to be good in both eyes In November 1969 the visual acuity of his left eye was found to be 0 ? He was admitted to our eye clinic in December 1969 Eye signs The visual acuity of the right eye was ? 0 and of the left eye 0 ? Refraction of both eyes was + 1 25 The right eye was normal The left optic disc showed a temporal crater with small vessels emerging from it (Fig 1) There was a circular detachment of the macula with a disc si ed diameter In the center of this cyst there was a macular hole with a net like covering (Fig ?) The perimetry revealed a defect extending from the enlarged blind spot almost to the fixation point In the stereophotographs the elevated retina in the macula and the crater of the optic disc were seen clearly Fluorescein angiography showed no leakage spots of vessels A sl ght choroidal fluorescence was seen through the pigment defects in the macula (Fig 3)

At first no treatment was given to this patient About six months later no changes were found in his left fundus Then 7 burnings of photocoagulation were done just at the temporal margin of the optic disc In a month the macular detachment was larger than before photocoagulation but the small burning scars were found near the papilla Two months after photocoagulation the macular detachment was large but lower than before and the v sual acuity was 0 4 parts At further re examinations the visual acuity

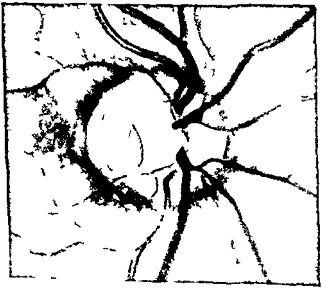


Fig 4

Ca e No II T The right optic d sc showed a deep central excavation near the temp ral margin f which was a deep oval optic pit (lined area)

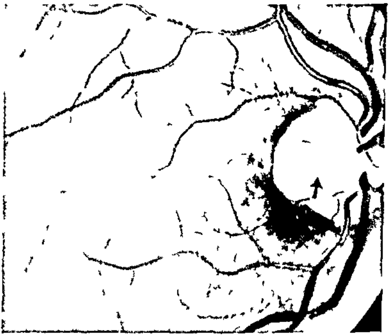


Fig 5

Case No 2 H T The macular detachment extended from the temporal margin of the macula to the optic disc The optic pit is shown with an arrow

varied a little but no oedema was found in the fundus About two years after the first examination the visual acuity was 0 4 parts Hardy Rand Rittler pseudo isochromatic test and Farnsworth dichotomous test Panel D 15 were normal There were pigmentary scars near the margin of the papilla and small white spots around the macula but no macular hole No oedema was found The field defect from the blind spot to the fixation point was very much as before

Case No 2

H T a 12 year old boy had had good sight in both eyes at the school examination one year earlier He had no subsequent subjective symptoms but at the following school examination the visual acuity of his right eye was unexpectedly found to be a little lower than that of his left eye The boy was admitted to our eye clinic in February 1970

Eye signs The visual acuity of the right eye was 0 8 With a correction of + 1 5 it was 1 25 The visual acuity of the left eye was 1 2, and with a correction of + 0 5 it was 1 75 The left eye was normal The right optic disc showed a deep central excavation and near the temporal margin of this excavation there was a deep crater like optic pit (Fig 4) The macular detachment was quite large extending from the temporal margin of the macula to the optic disc (Fig) Fluorescein angiography showed no leakage of vessels and no fluorescence was seen in the macular detachment The perimetry showed a relative central scotoma The adaptation curve was normal The colour tests (Hardy Rand Rittler pseudo isochromatic test Nagel anomaloscope

Ishihara test Bostrom Kugelberg and Bostrom pseudo isochromatic charts and Farns worth dichotomous test Panel D 15) were normal Electrooculography and electro retinography were normal

The boy was treated with corticosteroids for three weeks and the macular detach ment l wered gradually Photocoagulation was then performed at four places near the temporal margin of the optic disc After this therapy the reaction at the margin of the papilla was clearly seen but there was still fluid under the retina in the macula The patient was re examined many times afterwards and the visual acuity varied a little Pigmentary changes in the macula were reported about 17 months after photo coagulation. Two years after the first examination the visual acuity of the eye was 1 /5 The optic disc was unchan ed the macula had a lot of reflexes but there was no clear detachment The macula was a little yellow r than usual and was surrounded by small white spots The pigmentary scars were seen at the temporal margin of the ptic d sc

Case No 3

V K a 0 year old man, had noticed a shadow near the central point of vision of his left eye in November 19'9 This shadow gradually grew and the visual acuity deteriorated Straight lines began to appear oblique A diagnosis of retrobulbar neuritis was made at another eye clinic where the patient was treated twice with corticosteroids and B itamins for one month The visual acuity did not improve In February 1970 the patient was admitted to our eye cl nic



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Ca e N 3 V K The left pt c d sc sh wed a temp ral p t and a vessel emerging from t

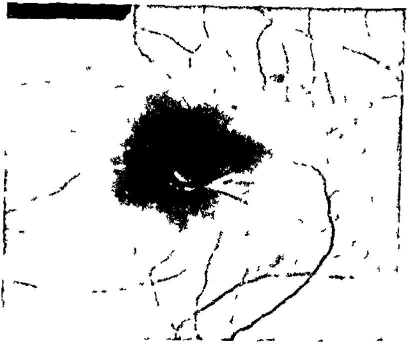


Fig 7
Case No 3 V K The left macula showed a quite large detachment with clover formed changes in the pigment epithelium



Fig 8
Case No 3 V K About one year after photocoagulation fluorescein angiography revealed intense fluorescence in the photocoagulation scars and a slight transmission of choroidal fluorescence in the macula

Eye signs The visual acuity of the right eye was 2 0 with a correction of −3 0 The visual acuity of the left eye was only finger counting at half a meter and the myopic correction did not improve the visual acuity The right eye was normal A temporal pit was found in the left optic disc and a vessel was emerging from the crater (Fig 6) Detachment of the macula with clover formed chan°es in the pigment epithelium was found (Fig 7) The perimetry showed a central absolute scotoma Fluorescein angiography showed no leakage of dye Stereophotographs revealed clearly the great elevation of the retina in the macula Colour vision was a little disturbed The adaptation curve was normal

The treatment with corticosteroids did not improve the condition Photocoagulation was performed half a year after the first symptoms with ten burnings at the temporal margin of the optic disc Follow up examinations showed that the visual acuity did not improve The patient was last examined about 14 months after photocoagulation The pigmentary scars were seen at the temporal margin of the optic disc The macula showed no detachment but there were atrophic and pigmentary changes Fluorescein angiography revealed intense fluorescence in the photocoagulation scars and a slight choroidal fluorescence appeared at the macula because of pigment defects (Fig 8)

Discussion

A total of approximately 1/5 pits in the optic disc have now been described in the literature and macular lesions have been detected in 60 of these (Gordon & Chatfield 1969) Many theories have been put forward to explain this association Various theories have also been reported about the nature of the pit itself The latest histopathological reports (Petersen 1958 Ferry 1963) have shown that the pit is filled with rudimentary retinal tissue associated with glial elements nerve fibres and pigment epithelium The defect is like a pocket in the papilla filled with aberrant tissue rather than a true hole The condition has been considered by most observers to be an atypical coloboma with a herniation of neuroectoderm into the nerve head at the margin of the optic disc

The characteristic features of the three cases now presented were similar to those of the other cases reported earlier The optic pit was situated temporally Visual field testing performed in all cases showed an absolute or relative central or paracentral scotoma Fluorescein angiographies showed no para macular spots of dye leakage such as occur in one type of central serous cho roidopathy Cass (1969) considered that photocoagulation at the rim of the optic pit could perhaps prevent a future recurrence of the detachment of the macula after the resolution of the subretinal fluid In our investigation two cases (No 1 and No 2) showed gradual improvement of the visual acuity after photocoagulation even though it was performed in the phase of macular oedema and not after a spontaneous resolution of the fluid In similar cases

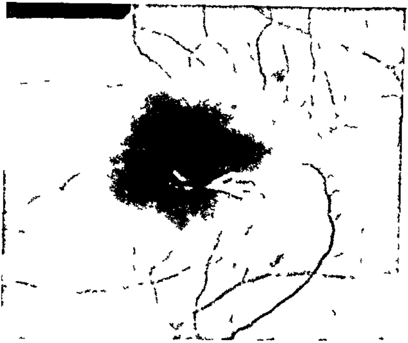


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Case No 3 V K About one year after photocoagulation fluorescein angiography revealed intense fluorescence in the photocoagulation scars and a slight transmission of choroidal fluorescence in the macula

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Discussion

A total of approximately 175 pits in the optic disc have now been described in the literature and macular lesions have been detected in 60 of these (Gor don & Chatfield 1969) Many theories have been put forward to explain this association Various theories have also been reported about the nature of the pit itself The latest histopathological reports (Petersen 1958 Ferry 1963) have shown that the pit is filled with rudimentary retinal tissue associated with glial elements nerve fibres and pigment epithelium. The defect is like a pocket in the papilla filled with aberrant tissue rather than a true hole The con dition has been considered by most observers to be an atypical coloboma with a herniation of neuroectoderm into the nerve head at the margin of the optic disc

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however, resolution of the subretinal fluid has been seen to occur without any treatment

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SYSTEMIC STEROIDS AND OCULAR FLUID DYNAMICS

III The Genetic Nature of the Ocular Response and Its Different Levels

BY

V FEILER-OFRY V GODEL and R STEIN

Topical dexamethasone tests performed on 13 patients receiving long term systemic steroids proved that the response also to this route of steroid administration is genetically determined and differs only quantitatively but not in principle from that to topical application. Pre systemic steroid values of ocular pressure and outflow facility of probands were calculated from data of the first degree relatives Systemic steroids produce in steroid responsive individuals pressure rises which average 60 % of those produced by topically applied steroids Systemic steroids reduce outflow facility by an average of 25 % while the reduction with topical steroids amounts to 60 %

Key words aqueous – steroids – heredity

Apart from some divergence in opinion on the mode of transmission of the differential hypertensive ocular response to topically applied steroids the genetic foundation of this phenomenon can today be regarded as fairly well established (Becker & Hahn 1961 Armaly 1966a b c) Very little is known however about the genetic basis of the ocular response to systemic steroids

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(Goldmann 1966) nor is there any knowledge of the different levels of response to systemic steroids The main obstacle to a satisfactory investigation of these questions is that it is impossible in patients suffering from severe general diseases but otherwise with healthy eyes to interrupt the steroid treatment for a sufficiently long period to reveal their steroid uninfluenced aqueous dynamics Only rarely is there a chance to study either a patient prior to commencement of systemic steroid therapy or one whose treatment had to be stopped for some reason (Goldmann 1966 Godel Feiler Ofry & Stein 1970) An indirect approach towards classifying patients on long term systemic steroids into steroid responders and non responders was to subject them to a topical dexamethasone test The results of such an investigation were reported in Part II of this study (Godel Feiler-Ofry & Stein 1972) The experiment did not however shed any light on the magnitude of the individual patient s response to systemic steroids

In studies of the genetic determination of ocular pressure and aqueous outflow facility Armaly (1967a 1968) managed to show a statistically significant *correlation of these two parameters in clinically normal eyes of first* degree relatives In view of this even considering the inherent discrepancies between theoretical and actual values resulting from non inherited sources of variability we hoped an investigation of the first degree relatives of our probands would provide measures which might permit conclusions on the base line pressures and tonographic values existing in the probands prior to the start of treatment with systemic steroids For this purpose we recruited as many of the first degree relatives of the patients as we could however as the value of studying the relatives was *recognized only after the conclusion of the main investigations* we succeeded only in recruiting the family members of a relatively small number of probands

Sample and Procedure

First degree relatives of *13* patients (probands) who were receiving *long* term treatment with systemic steroids were recruited for the study The sample comprised 48 individuals not counting the probands The composition of the sample with regard to number of families sex and type of relation to the proband is listed in Table I If proband was a parent only the data of the offspring were used for statistical evaluation and not those of the spouse whose data served only as a check on the statistics of the offspring Four of the probands were younger than 20 years the youngest being a , year old boy suffer

Table 1
Sample composition

	Proband		Parent		Offspring		Sibling		Spouse		
No of families	M	F	M	F	M	F	M	F	M	F	Total
13	5	8	5	6	16	7	3	4	3	4	61

ing from rheumatic arthritis 4 probands were in the age group of 36 to 42 years and the remaining 5 were older than 50 years the oldest being 64 years Among the family members 5 (2 offspring and 3 siblings) were younger than 20 years the ages of 31 (5 parents 21 offspring and 5 siblings) were between 24 and 46 years and the remaining 4 parents were over 55 years old

When the family members reported for the study their family s and their own medical and ocular histories were verified They then underwent the same ocular examination as described in Part I of this study After tonometry by applanation and tonography they were instructed to put 0 1 % ophthalmic solution of dexamethasone into their right eye 3 times daily Tension was checked every week at the same hour of the day and after 4 weeks a second tonography was performed C values were corrected when the difference be tween applanation and Schiotz readings was greater than 2 mmHg

Results and Discussion

The results of the dexamethasone provocative test performed on the 6 steroid non sensitive and 7 steroid sensitive probands and on their first degree relatives are shown in Figs 1 and 2 respectively The classification according to the different levels of pressure rise following the topical application of dexa methasone was based on the criteria proposed by Armaly (1966b) Individuals with a pressure rise of up to 5 mmHg were typed as non or low responders those with a pressure rise from 6 to 15 mmHg as intermediate and those with elevations of more than 15 mmHg as high responders If these three levels of response represent phenotypes of three genotypes resulting from the combina tion of the two alleles P^L (for low magnitude of pressure rise) and P^H (for high magnitude of pressure rise) (Armaly 1967b) then this study of first degree

(Goldmann 1966) nor is there any knowledge of the different levels of response to systemic steroids The main obstacle to a satisfactory investigation of these questions is that it is impossible in patients suffering from severe general diseases but otherwise with healthy eyes, to interrupt the steroid treatment for a sufficiently long period to reveal their steroid uninfluenced aqueous dynamics Only rarely is there a chance to study either a patient prior to commencement of systemic steroid therapy or one whose treatment had to be stopped for some reason (Goldmann 1966, Godel Feiler-Ofry & Stein 1970) An indirect approach towards classifying patients on long term systemic steroids into steroid responders and non responders was to subject them to a topical dexamethasone test The results of such an investigation were reported in Part II of this study (Godel Feiler Ofry & Stein 1972) The experiment did not however shed any light on the magnitude of the individual patient s response to systemic steroids

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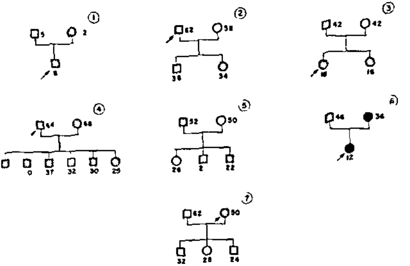


Fig 2

Family trees of steroid sensitive probands treated with long term systemic steroids Family members according to topical dexamethasone test low or non responders (white symbols) intermediate responders (cross hatched symbols) and high responders (black symbols)

this dilemma however One was his finding (1967a) that the ocular pressure level in the clinically normal eye is genetically determined and that the ocular pressures of first degree relatives show a highly significant correlation He arrived at the same conclusions with regard to outflow facility values (Armaly 1968) In order to eliminate from our calculations the known influence of age and sex on ocular pressure and outflow facility we used Armaly s corrections (1967c) to transform to standard scores the measured raw scores of probands first degree relatives and re calculated from these standard scores the pre sumable pre systemic steroid values of the probands Since the allele pair P^L P^H is one of the major factors involved in the genetic determination of ocular pressure and outflow facility though not the only one (Armaly 1968) our calculations of the probands pre treatment raw scores used only the data of those first degree relatives who were of the same genotype We are fully aware of the fallibility of such an undertaking in view of the dependence of the parameters in question not only upon hereditary factors but also upon many non heritable sources of variability including environment (Armaly 1968) further our sample was relatively small and in two families it was even impos sible to get more than one family member of the same genotype on which we

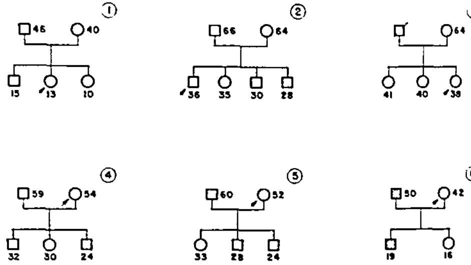


Fig 1

Family trees of steroid non sensitive probands treated with long term systemic steroids Family members according to topical dexamethasone test low or non responders (white symbols) intermediate responders (cross hatched symbols)

relatives whose phenotypes were determined should reflect the genetic determination of the three magnitudes of response to topical steroids as well as the mode of their hereditary transmission An inspection of the genealogic trees of the non or low responding probands illustrated in Fig 1 shows that all first degree relatives were of the same phenotype in respect to the level of response to topical dexamethasone as the probands themselves with the exception of the son of proband (6) who was an intermediate responder having inherited the allele P^H from his father the husband of the proband Of the steroid sensitive probands whose family trees are exhibited in Fig 2 11 first degree relatives were steroid responders and 9 were non responders Proband 6 a 12 year old girl was the only high responder in this group having inherited both alleles P^H from her father who was an intermediate responder and her mother a high responder A check of all the genealogic trees shows that topical steroid testing of our sample brought to light all three possible combinations of the two alleles P^L and P^H and that no case contradicted the assumption of a Mendelian dominant autosomal inheritance of the responsivity to topical steroids

Having established the genetic nature of the topical steroid ocular response however we still could not answer the question of whether the ocular response of the probands to systemic steroids was commensurable or determine the order of this response since we still did not know the steroid uninfluenced values of their ocular fluid dynamics Two facts established by Armaly helped us out of

Table III

Percental change in outflow facility following systemic and combined systemic and topical steroid treatment in 6 steroid non sensitive and 7 steroid sensitive probands compared to the change in outflow facility due to topical steroid in their 19 non sensitive and 19 sensitive first degree relatives (Mean±standard deviation)

	C_{yst}/C_{cal}	$C_{yst\ top}/C_{yt}$	$C_{syt\ top}/C_{alc}$	C_4/C_0
Non responders	1 16±0 28	0 93±0 18	0 80±0 29	0 92±0 21
Responders	0 74±0 15	0 61±0 13	0 42±0 19	0 41±0 23

C_{calc} Outflow facility before systemic steroid administration calculated from data of probands first degree relatives

C_{yst} *Outflow facility in probands receiving long term systemic steroids*

$C_{yt\ top}$ Outflow facility after 4 weeks of topical dexamethasone application in probands receiving long term systemic steroids

C_4/C Rate of change in outflow facility after 4 weeks of topical dexamethasone application in probands first degree relatives

suggests the possibility of at least two partially different mechanisms of the ocular pressure rise following systemic and topical administration of steroids respectively

Our experimental and calculated data showed that in steroid sensitive individuals the pressure rise following systemic administration of steroids is on an average about 60 % of that effected by topical steroids The limits of the pressure rises elicited by *systemic steroids* and the delineation of the 3 levels of pressure rise are therefore up to 3 5 mmHg for low from 4 to 9 mmHg for intermediate and more than 9 mmHg for high steroid responders

Investigations and calculations analogous to those for pressure changes were made for changes in outflow facility (Table III) Following systemic steroid administration the outflow facility in the non responder group did not show any reduction and there was even an increase of the mean C value by about 16 % *in this group* In the group of responders systemic steroids reduced the mean C value by about 25 % Additional *topical steroid* elicited a further decrease of C to about 40 % of the calculated pre systemic steroid value In the first degree relatives the outflow facility dropped by about the same amount after topical dexamethasone It is evident that steroids coming to the eye by the systemic route reduce outflow facility in susceptible persons but this reduction averages about 25 % while with topically applied steroids the reduction is more than twice as much Though pressure rises elicited by systemic steroids may

could base our calculations of the proband s data In spite of these uncertainties and the roughness of the calculated figures the results of our investigation seem quite reasonable

Table II shows the mean pressure rise over the calculated pre systemic steroid values (P_{calc}) after treatment with systemic steroids and with combined systemic and topical steroids and compares this with the pressure rise due to topical dexamethasone in the probands first degree relatives of the same genotype No significant change in pressure following long term systemic steroids took place in the steroid non responders In the responders on the other hand systemic steroid elicited a mean pressure increase of 6 8 mmHg with a standard deviation of ± 3 5 mmHg Additional application of topical dexamethasone for 4 weeks was followed by a further pressure increase of 10 7±4 5 mmHg The pressure elevation due to topical dexamethasone in the probands who were on systemic steroids was of about the same order as that found in the probands first degree relatives who had the same genotype *From this fact one may conclude that the pressure rise following topical application of steroid is not influenced by the pressure rise already present and due to systemic steroids This independence of pressure elevations from each other*

Table II

The magnitude of pressure change due to systemic and combined systemic and topical steroids in 6 steroid non sensitive and 7 steroid sensitive probands compared to pressure changes due to topical steroids in their 19 non sensitive and 12 sensitive first degree relatives (Mean±standard deviation)

	Pressure rise (mmHg)			
	$P_{syst}-P_{calc}$	$P_{syst+top}-P_{syst}$	$P_{syst+top}-P_{calc}$	P_4-P
Non responders	1 2±2 35	1 05±1 02	2 2±2 31	0 94±3 12
Responders	6 8±3 50	10 7 ±4 50	17 5±4 51	9 0 ±3 71

P_{calc} Applanation pressure of probands before systemic steroid treatment calculated from data of their first degree relatives

P_{yst} Applanation pressure due to long term systemic steroids

$P_{syst+top}$ Applanation pressure after 4 weeks of topical dexamethasone in probands taking systemic *steroids*

P_0 Applanation pressure in first degree relatives of probands

P_4 Applanation pressure after 4 weeks of topical dexamethasone application in probands first degree relatives

From the Department of Experimental Ophthalmology Institute of Pharmacology (Head Prof Ernst Barány) University of Uppsala Sweden

EFFECTS OF NOREPINEPHRINE ANGIOTENSIN DIHYDROERGOTAMINE PAPAVERINE ISOPROTERENOL HISTAMINE NICOTINIC ACID AND XANTHINOL NICOTINATE ON RETINAL OXYGEN TENSION IN CATS

BY

ALBERT ALM

The oxygen tension in the vitreous body close to the retina P_{rO_2}, was determined continuously in cats The effects on P_{rO_2} of intraarterial injections of various vasoactive drugs were determined The vasoconstrictors norepinephrine angiotensin and dihydroergotamine did not change P_{rO_2} in five cats The same result was obtained with the vasodilators isoproterenol histamine and xanthinol nicotinate in five cats and with nicotinic acid in six cats while papaverine invariably increased P_{rO_2} in seven cats when injected intraarterially and in two cats when injected intravenously It is suggested that the ability to penetrate the blood retinal barrier may play an important role in determining the effect of vaso active drugs on retinal blood flow

Key words norepinephrine – angiotensin – dihydroergotamine – papaverine – isoproterenol – histamine – nicotinic acid – xanthinol – nicotinate – retinal oxygen tension – blood retinal barrier

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be partly due to reduced C values this reduction does not fully account for pressure rises which are about 60 % of those elicited by topical steroids This discrepancy intimates the role which increased formation of aqueous humor due to action of systemic steroids may play in the production of elevated ocular pressures in steroid sensitive persons treated with systemic steroids

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of a 1% solution of chloralose 50–70 mg/kg b w and urethane as needed The femoral artery and vein on one side were cannulated with polyethylene catheters the vein for injections and the artery for measurements of the air damped MAP with a pressure transducer (EMT 490 A Elema Schonander Solna Sweden) The thyroidal artery on one side was cannulated with a thin polyethylene catheter pushed into the carotid artery usually with the tip pointing towards the heart All animals were tracheotomized and artificially ventilated with a Palmer pump Arterial P_{O} P_{CO_2} and pH were determined with a Beckman Physiological Gas Analyzer Model 160 The animals were placed supine on a heating pad with the neck gently rotated and the head kept in a head holder at about a 90 angle to the body The body temperature was determined with a rectal thermometer and usually was kept within 2° of 38 5 C

The method for determining P_{vrO} has been described in detail previously (Alm & Bill 1972a) The anterior chamber of the eye on the same side as the cannulated thyroidal artery was cannulated with a steel needle connected to a pressure transducer (FMT 490 A) for measurements of the actual IOP and also connected with an external reservoir filled with mock aqueous humor for stabilization of the IOP (Bárany 1964) The oxygen electrode (Beckman micro oxygen electrode) was inserted through the sclera into the vitreous body with the tip less than 2 mm from the retinal surface and usually within 8 mm of the papilla P_{rO} IOP and MAP were recorded continuously on a multi point recorder (Philips PR 3212 A/00)

The following drugs were given i a norepinephrine (Nor exadrin conc® ACO) angiotensin (Hypertensin N® Ciba) dihydroergotamine (Orstanorm® Sandoz) papaverine (Papaverin® ACO) isoproterenol (DL Isoproterenol HCl Sigma) histamine (Histamin® ACO) nicotinic acid (Nikotinsyra® ACO) and xanthinol nicotinate (Complamin® Tika) In two cats which had previously been subjected to stimulation of the distal end of the divided cervical sympathetic chain papaverine was injected i v The drugs that were administered i a were injected in small volumes during a 10 minute period The volume was between 0 5 and 2 0 ml totally and this was given in 10 or more small rapid injections to ensure that the drugs reached the retinal vessels The concentration was chosen so that clear but rapidly recovering effects on the MAP were seen from the single injection for norepinephrine angiotensin papaverine isoproterenol and histamine Dihydroergotamine and nicotinic acid were given in doses similar to those used previously for determining the effect on the uveal vascular resistance in cats (Bill 1962) For xanthinol nicotinate the total dose was 10 mg

Before and after injections of the drugs the estimated distance from the

In tissues with autoregulation of blood flow physiological mechanisms tend to keep blood flow at an optimal level This implies that in situations where the arterial perfusion pressure is reduced the blood flow is not reduced until at least a large part of the potential vasodilatation has occurred As a consequence pharmacological blood flow has only limited possibilities to increase blood flow in such tissues if vasodilatation has been reduced by factors other than increased vascular tone e g partial occlusion of an artery In fact vasodilators may even reduce blood flow through ischemic tissues by reducing the arterial perfusion pressure (Brawley 1968, Lassen & Westling 1969)

For the retina the situation is more complicated than in most tissues since it is nourished by two independent vascular beds the choroidal and the retinal vessels We therefore need to know the physiological and the pharmacological regulation of both these vascular beds in order to get a complete picture of the effect of vasoactive agents on the nutrition of the retina We know that autoregulation of blood flow is present in the retina but not in the choroid moderate reductions in the perfusion pressure defined as the mean arterial blood pressure (MAP) minus the intraocular pressure (IOP) result in unchanged or even increased blood flow through the retina while that through the choroid is reduced in proportion to the reductions in perfusion pressure (Alm & Bill 1972b) We also know that several drugs may change the choroidal blood flow in laboratory animals (Bill 1962 Chandra & Friedman 1972) but the effect of these drugs on the blood flow through the retina is largely unknown due to the previous lack of suitable methods for determining retinal blood flow Recently continuous determination of the oxygen tension in the vitreous body close to the retina P_{vO_2} has been used as a semiquantitative method for determining changes in retinal blood flow (Alm & Bill 1972a) Since this method gives information about changes in blood flow it can be used for studying indirectly the effects of vasoactive drugs on retinal blood flow The fact that the rationale for using vasodilating drugs is to improve the nutrition makes measurements of tissue P_{O_2} a more pertinent parameter than rate of blood flow The present investigation was undertaken to determine the effects of some vasoactive agents administered closely intraarterially (i a) on P_{vO_2} in cats

Methods

Eighteen adult cats of both sexes weighing between 2 1 and 3 9 kg were used Anesthesia was induced with chloroform and maintained with i v injections

of a 1% solution of chloralose 50–70 mg/kg b w and urethane as needed The femoral artery and vein on one side were cannulated with polyethylene catheters the vein for injections and the artery for measurements of the air damped MAP with a pressure transducer (EMT 490 A Elema Schonander Solna Sweden) The thyroidal artery on one side was cannulated with a thin polyethylene catheter pushed into the carotid artery usually with the tip pointing towards the heart All animals were tracheotomized and artificially ventilated with a Palmer pump Arterial P_O P_{CO} and pH were determined with a Beckman Physiological Gas Analyzer Model 160 The animals were placed supine on a heating pad with the neck gently rotated and the head kept in a head holder at about a 90° angle to the body The body temperature was determined with a rectal thermometer and usually was kept within 2° of 38 5°C

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Before and after injections of the drugs the estimated distance from the

retinal surface as well as the possibility to register changes in the oxygen tension in the retina were tested by ventilating the cat for 1–3 min with 6 5 % CO_2 in O_2 (see Alm & Bill 1972a) If later in the experiment this test failed to cause a marked increase in the P_{vrO_2} only drug tests that had been performed before or just after a previous positive test with 6 5 % CO_2 in O_2 were accepted Changes in the P_{vrO_2} of less than 2 mmHg or for a P_{vrO_2} of more than 20 mmHg less than 10 % of the original value were interpreted as showing that the drug had no effect on the P_{vrO_2} All drugs were tested in at least five cats and each drug was the first one tested in at least one experiment From 1–6 drugs were tested in each cat the number usually being 4 or 5

For some of the drugs the buffer/chloroform partition coefficient at a physiological pH was measured This coefficient was calculated from the concentration of the substance in 0 1 M phosphate buffer pH 7 4 before and after shaking for at least 1 hr with an equal volume of chloroform The initial concentrations of the substances were 50–150 μg/ml buffer Both buffer and chloroform were bubbled with nitrogen before use All measurements were based on the absorption at wave lengths between 230 and 280 μm

Results

The following data were obtained before injection of the first drug MAP 183 ± 6 cm H_2O (n = 18) stabilized IOP 29 ± 1 cm H_2O (n = 18) P_{vrO_2} 31 ± 2 mmHg (n = 18) arterial P_{O_2} P_{CO_2} and pH 99 ± 2 mmHg (n = 18) 28 ± 1 mmHg (n = 18) and 7 50 ± 0 2 units (n = 18) respectively The values are mean ± SEM

Drug effects on the oxygen tension close to the retina P_{vrO_2}

Fig 1 shows the effect of papaverine on P_{vrO_2} About 8 mg injected i v in two cats *and 2–20 mg injected i a in seven cats all resulted in* a clear increase in P_{vrO_2}

Fig 2 shows the effects of i a injections of 50 mg nicotinic acid on P_{vrO_2} in 6 experiments Although there was a slow reduction of about 3 mmHg in two cats the mean result indicates that nicotinic acid generally does not decrease P_{vrO_2} and it certainly does not increase it

No changes in P_{vrO_2} were seen after i a injections in five cats of 6–20 μg norepinephrine 1–20 μg angiotensin 200 μg dihydroergotamine 4–15 μg isoproterenol 7–13 μg histamine or 10 mg xanthinol nicotinate

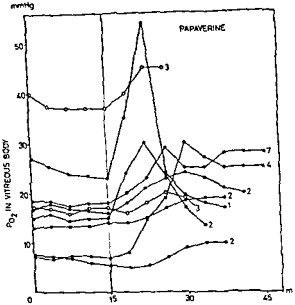


Fig 1

The oxygen tension in the vitreous body close to the retina P_{rO_2}, was continuously determined while papaverine was injected into the homolateral carotid artery in seven cats and into one femoral vein in two cats The vertical line represents the starting time of the injections The total dose in mg/kg b w is given for each experiment Curves with unfilled symbols represent intravenous injections curves with filled symbols represent intraarterial injections

Table 1

The buffer/chloroform partition coefficient and the effect on P_{rO_2} of some vasoactive drugs

Drug	Buffer/chloroform partition coefficient	Effect on P_{rO}
Papaverine	$<$ 0 1	+
Dihydroergotamine	$<$ 0 1	0
Norepinephrine	$>$ 10	0
Isoproterenol	$>$ 10	0
Histamine	$>$ 10	0
Nicotinic acid	$>$ 10	0
Xanthinol nicotinate	$>$ 10	0

The buffer was a 0 1 M phosphate buffer pH 7 4

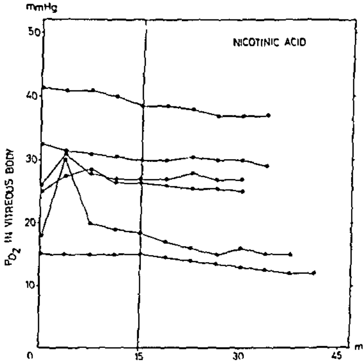


Fig 2
The effect of intraarterial injections of 50 mg *nicotinic acid on* P_{vrO} *in six cats*
The vertical line indicates the start of the injections

Table I presents the buffer/chloroform partition coefficient for the drugs tested in this respect The effects on P_{vrO} are also shown Papaverine and dihydroergotamine both had partition coefficients clearly below 0 1 indicating a relatively high lipid solubility while norepinephrine isoproterenol histamine nicotinic acid and xanthinol nicotinate had partition coefficients above 10 indicating a low lipid solubility

Discussion

P vrO2 and retinal blood flow

Previous attempts to determine drug effects on retinal *circulation generally* have been based on inspections of the diameters of retinal vessels (Porsaa 1911 Huerkamp & Rittinghaus 1950 Thuransky 1957 Dollery Hill & Hodge 1963) However Frayser & Hickam (1964 1965) combined vessel diameter measurements with determinations of retinal arterio venous oxygen differences which give information similar to that obtainable with P_{vrO} measurements and they

found that changes in vessel diameter give an unreliable estimate of changes in retinal blood flow

A change in P_{rO} does not always reflect a change in retinal blood flow it may be caused by a change in retinal oxygen consumption Isoproterenol has been reported to increase both oxygen consumption and blood flow in the brain (Purves 1972) and the effect on tissue P_O in such a situation is difficult to predict Thus it is possible that in the experiments with isoproterenol in the present study the unchanged P_{rO} conceals a concomitant rise in blood flow and oxygen consumption in the retina There is no obvious reason to suspect that the other drugs used in the present study change the metabolic rate of the retina cerebral oxygen consumption has been shown to be unaffected by administrations of norepinephrine (King Sokoloff & Wechsler 1952) papa verine (Jayne et al 1952) histamine (Shenkin 1952) and nicotinic acid (Schein berg 1950) while there seem to be no reports on the effect of angiotensin xanthinol nicotinate or dihydroergotamine on cerebral or retinal metabolism Thus it is likely that with the possible exception of isoproterenol the retinal blood flow response to the injected drugs was similar to that of P_{rO}

Vasoconstrictors

None of the vasoconstrictors used in the present study changed the P_{rO} Dihydroergotamine is only a weak vasoconstrictor also in other vascular beds in the brain blood flow seems to be reduced only if it initially had been increased by some other factor (Carpi 1972) in the cat uvea the increase in vascular resistance was not consistent (Bill 1962) and in skeletal muscle vaso constriction takes place mainly in the postcapillary capacitance vessels with only small changes in the total vascular resistance (Mellander & Nordenfelt 1970) Norepinephrine and angiotensin on the other hand are two of the most potent biogenic vasoconstrictors known Both however have effects on cerebral blood flow that are less pronounced than in peripheral tissues but at least norepinephrine seems to be able to reduce cerebral blood flow in spite of an increase in MAP (Carpi 1972) which speaks in favour of a direct action on the vessels Thus i a injections of norepinephrine seem to have smaller effects on retinal than on cerebral circulation and they also seem to have smaller effects on retinal circulation than stimulation of the cervical sympathetic chain since sympathetic stimulation reduces P_{rO} in cats (Alm & Bill 1973b)

Vasodilators

Papaverine was the only drug that increased the P_{rO}. The results suggest a marked vasodilatory effect in the retina Ellis & Lende (1964) found that papaverine applied locally on retinal vessels of the cat *in vivo* caused vaso

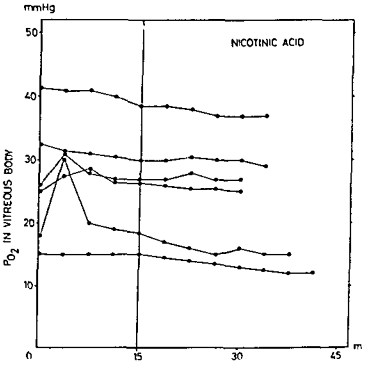


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degree of ionization and the lipid solubility of the undissociated molecule (Mayer Maickel & Brodie 1959) It seems reasonable that this is also the case for the blood retinal barrier Of the drugs that have been tested for their effect on P_{rO_2} in the present study only papaverine and dihydroergotamine have a lipid solubility at a physiological pH that suggests a relatively free passage through the blood retinal barrier (Table I) The lipid solubilities of norepinephrine isoproterenol histamine nicotinic acid and xanthinol nicotinate are low and therefore these drugs can be expected to have difficulties in penetrating the barrier This is also the case for angiotensin which is an octapeptide For norepinephrine and isoproterenol a further barrier is constituted by the presence of monoaminooxidase in the capillary endothelial cells (Bertler et al 1966)

If the blood brain and the blood retinal barriers prevent some vasoactive agents from reaching the vascular smooth muscle it means that the distal part of the resistance vessels is not directly influenced by these drugs Thus a change in resistance of the proximal part of the vascular bed induced by a drug that does not penetrate the barrier will initiate a change in the other direction in the distal part of the vascular bed through autoregulatory mechanisms Then the effect of such a drug on total vascular resistance will depend on initial tone of the distal vessels Factors such as MAP anesthetic depth and degree of surgical trauma may influence vascular tone and may thus explain the contradictory results of different studies on the effects of vasoactive agents on cerebral blood flow

If we assume that the barriers exist in vessels surrounded by nervous tissue they can be expected to protect a larger part of the retinal vessels than of the brain vessels since the retinal arteries i cats are 30–50 μm when they enter the eye (Porsaa 1941) while the pial vessels are only about 25 μm when they enter the grey matter (Shapiro et al 1971) This may explain a possible difference between the cerebral and the retinal circulations in resistance to changes induced by vasoactive drugs It may also explain the difference between stimulation of the cervical sympathetic chain and i a injections of norepinephrine on the effect on P_{rO_2} since the retinal arteries of the cat are sympathetically innervated also in their intraneural part up to the lamina cribrosa (Laties & Jacobowitz 1966)

The fact that the lipid soluble drug papaverine which is considered to be a weak vasodilator in extraneural tissue (Goodman & Gilman 1970) seems to be one of the more potent vasodilators within the central nervous system agrees well with the concept that the blood brain and blood retinal barriers are factors determining the effect of vasoactive drugs However other possible explanations for the resistance of retinal and cerebral blood flow to changes

dilation and in the brain papaverine increases blood flow in both man (Jayne et al 1952) and dog (Häggendal 1965) Frayser & Hickam (1965) however found that i v injections of 64 mg papaverine in humans had no effect on the arterio venous oxygen difference or vessel diameters in the retina Differences in dose levels may explain the discrepancy between the results of this investigation and those of the present study

As pointed out above isoproterenol seems to increase cerebral blood flow possibly secondary to an increase in cerebral metabolic rate Histamine is a weak vasodilator in the brain while nicotinic acid and xanthinol nicotinate have negligible effects on cerebral blood flow (Carpi 1972) They do not seem to be more effective in the retina

Drugs and the blood retinal barrier

Previous studies on the physiological regulation of retinal circulation in cats and monkeys have indicated that there are many similarities between the retina and the brain (Porsaa 1941 Alm & Bill 1972a b 1973) The present results indicate that also the vascular pharmacology of the retina is best compared to that of the brain the cerebral circulation usually shows small and variable responses to drugs that affect blood flow in other parts of the body (for reviews see Sokoloff 1959 Carpi 1972)

A characteristic of the retina as well as of the brain which may explain the reaction of these vascular beds to vasoactive drugs is the existence of barrier mechanisms preventing passage of some substances from blood into tissue For the retina these barriers are the blood retinal barrier in the retinal vessels on the one side and the retinal pigment epithelium on the other (Shiose 1971) In rats the vascular endothelial cells and their tight junctions were considered to constitute the blood retinal barrier to large molecular aggregates such as trypan blue and colloidal carbon (Cunha Vaz Shakib & Ashton 1966) Bertler et al (1966) have studied the barrier mechanism for catecholamine precursors in the mouse brain They found that d dopa which is not carried by the stereospecific amino acid pump and dopamine penetrated into the media of ...al vessels but were almost completely prevented from penetrating into the endothelial cells of the vessels inside the parenchyma in areas with a blood brain barrier and the same is true for the intraocular part of the retinal vessels in cats (Ehinger personal communication) Thus the barrier for these drugs is not restricted to the capillaries but exists in the arterioles as well and it is likely that the retinal vascular endothelium constitutes a barrier between blood and vascular smooth muscles also for some other drugs

The blood brain barrier has the characteristics of a lipid membrane and the factors that determine passive passage of drugs through the barrier are the

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induced by drugs must be kept in mind the efficient autoregulation may prevent changes induced by pharmacological agents or the vascular smooth muscles of these vessels may lack receptors for some drugs The first possibility implies that papaverine eliminates autoregulation this is not the case in the brain of the dog where papaverine increases blood flow but autoregulation remains although within a smaller range (Ekström Jodal Häggendal & Nilsson 1970) The other possibility can only be tested in experiments where the drugs are applied outside the barrier or where the barrier is destroyed

Vasodilators and reduced retinal blood flow

The present investigation indicates that several drugs that do change the blood flow through other tissues including the choroid do not increase blood flow through the retina Papaverine is one exception and there may be others The fact that the choroidal vascular bed which has a normal blood flow 25–50 times that through the retina lacks autoregulation should make the retina unusually susceptible to an "intraocular steal syndrome Drugs that dilate the choroidal vessels will cause marked increases in blood flow through the ophthalmic artery and thereby reduce the arterial pressure at the point of origin of the retinal artery which tends to reduce retinal blood flow Normally autoregulation may prevent a reduction in retinal blood flow but in an ischemic retina autoregulation is already utilized and the blood flow through the retina is further reduced It is unlikely that the increase in choroidal blood flow is an adequate compensation Drugs such as papaverine which have an effect on retinal *circulation may be useful only if they can dilate the vessels further* when autoregulatory vasodilatation is maximal Studies on the effect of vasodilators on P_{rO} in eyes with marked reductions in perfusion pressure will help to elucidate these problems To the statement of Havener (1970) I can see no reason (other than placebo) for the use of vasodilators in the practice of ophthalmology perhaps should be added that some vasodilators may have clearly negative effects in disorders with reduced retinal blood flow

It is of possible clinical interest however that the choroid in contrast to many other vascular beds lacks autoregulation and responds to vasodilators The susceptibility of the optic nerve head to moderate increments in the IOP has been suggested to depend on the lack of autoregulation in the choroid (Alm & Bill 1973a) Thus theoretically vasodilators may have a beneficial effect on optic nerve head blood flow at moderate increments of the IOP At present it is *difficult to predict which change will be the most important* for the optic nerve head – the reduction in vascular resistance in the arterioles outside the nerve head or the reduction in perfusion pressure

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1 INTRODUCTION

One main disadvantage of Grant s method of tonography(4) is the decrease in intraocular pressure during the procedure During the application of this method the rate of aqueous flow facility of outflow episcleral venous pressure and intraocular blood volume may change It is however not possible to estimate the extent of these changes which has limited the clinical usefulness of regular tonography These problems as well as the advantages and technical possibilities of obtaining a tonography at constant intraocular pressure were discussed by Linnér & Thorburn(6) As one method of attacking this complex set of problems these authors proposed the use of continuous measurement of intraocular pressure and applanating force

In practice such measurements may be carried out with an apparatus based on the following general principle One wall of a pressure chamber is used as an applanating surface the central part of which has an aperture The surface and its aperture are covered with a flexible membrane During applanation of the cornea the curvature of the part of the membrane covering the aperture indicates any difference in pressure between that in the pressure chamber and that in the eye Disregarding the cornea s resistance to deformation equal pressures in the eye and the chamber result in no curvature of the membrane The applanating force is regulated by means of an electrical signal indicating the degree of curvature of the flexible membrane In this way it is possible to keep the applanating force continually adjusted while at the same time the intraocular pressure is kept constant at a predetermined value in principle equal to the pressure in the pressure chamber

By measuring the applanating force and knowing the intraocular pressure the applanated area can be calculated This calculation is generally based on the relationship called the Imbert Fick law (applanating force = intraocular pressure × applanated area) Goldmann & Schmidt(2) pointed out the effects of corneal resistance against deformation and the influence of surface tension According to them these two phenomena cause forces acting in opposite directions They found that the forces cancel each other out at an applanation diameter of 3 mm but probably not over larger areas Moses & Tarkkanen(8) using applanation diameters between 4 9 and 7 6 mm did not find any consistent deviation from the Imbert Fick law Goldmann & Schmidt(3) investigated applanated areas from 3 to 7 mm diameter and found a small deviation from the Imbert Fick law showing that the measured pressure in the eye was slightly less than that calculated Gloster & Perkins(1) measured the applanation diameter the intraocular pressure (P) and the applanating force (W) With A (applanated area) equal to $a + b \times W/P$ a linear regression of A on

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RECORDINGS OF APPLANATING FORCE AT CONSTANT INTRAOCULAR PRESSURE

I Basic principle and apparatus description

BY

WILLIAM THORBURN

An apparatus designed for continuous recording of applanating force at constant intraocular pressure is described The applanating surface is a wall of a pressure chamber the central aperture of which is covered with a flexible membrane A pressure difference between the eye and the pressure chamber is indicated by a curvature of this membrane An electric signal indicating the degree of curvature of the membrane controls the applanating force. Calibration studies on enucleated human eyes of the relationship between the intraocular pressure and the pressure in the pressure chamber are performed The results and methodological errors are discussed with regard to possible future use of the apparatus in experiments on living human eyes

Key words applanation – constant intraocular pressure – force recording – intraocular pressure – pressure measuring apparatus

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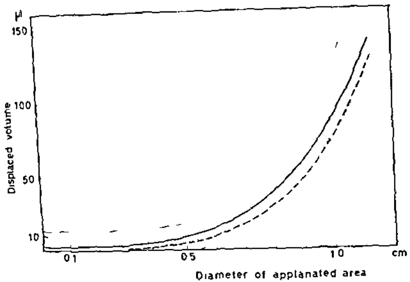


Fig 1
The relationship between applanated area (abscissa) and the volume displaced by applanation calculated as a spherical segment (dashed line) and according to the experimental results of Linner(5) (solid line) From Linner(5) with the permission of the author

posterior hemisphere of the globe obtain a more spherical shape with an un changed or even increased intraocular volume On the other hand no change in the total length of the living eye could be detected by means of ultrasonic echograms at an applanation of 6 mm diameter(12 13)

The displaced volume calculated as a spherical segment probably represents the lower limit value and the results of Linnér(5) the upper limit value These two relationships between displaced volume and applanated area are shown in Fig 1 It is not known if applanation of the cornea also causes additional defor mations in the living eye In the present investigation the displaced volume is calculated as a spherical segment with the base equal to the applanated area and 7 8 mm as the radius of the corneal curvature This method of calculation results in arbitrary units giving the possibility to estimate the displaced volume

2 APPARATUS

A schematic diagram of the apparatus is shown in Fig 2 The pressure chamber described in detail below is mounted at the lower end of an aluminium T arm

W/P was calculated They found the flattened area of the cornea smaller than that expected from the theoretical relationship The mean of nine corneas was $A = 0.70 + 62.0\ W/P$, (A is expressed in mm² W in g and P in mmHg) to be compared with the expected $A = 0 + 73.5\ W/P$ The departure from the Imbert Fick law varied from cornea to cornea Linnér(5) obtained similar results the mean of the experiments being $A = 0.45 + 62.2\ W/P$ With different eyes different values of the a and b were obtained

The results from the above investigations suggest a deviation between the measured applanated area and that calculated from applanating force and intraocular pressure in measurements on enucleated human eyes The calculation of large applanated areas (> 3 mm diameter) from intraocular pressure and applanating force may imply a small proportional overestimation The error is probably of different size in different eyes due to varying properties of different corneas It is not known to what extent this is true *in vivo* The present study refrains from introducing any corrections

The volume displaced by the applanation (which below is termed the displaced volume) is related to the applanated area In a first approximation this relationship can be calculated as if the displaced volume is a spherical segment with the base area equal to the applanated area Investigations by Stepanik(10) show that the inner surface of the cornea follows the applanation of the outer surface Furthermore he found no detectable change in the curvature of the surrounding cornea during applanation up to 6 mm diameter compared with that in the untouched eye(10 11) Gloster & Perkins(1) studying human corneas found that the volumes of fluid displaced by applanation were in general agreement with those calculated as spherical segments using the external radius of the corneal curvature in the calculation

The application of an applanating force against the cornea results in a counter force acting on the posterior part of the eye This probably results in an additional deformation of the eye besides the applanation of the cornea This idea is supported by the following reports Moses(7) performing measurements on four enucleated human eyes mounted in an artificial orbit by measuring the liquid displaced by applanation from the canulated eye found the displaced volume to be 17 % greater than that calculated as a spherical segment The applanated area was calculated according to the Imbert Fick law i e the results include the error of this way of calculation Measurements by Linner(5) in a similar way on enucleated eyes during applanation showed larger volumes than those calculated as spherical segments when the measured applanation diameter was used for the calculation The volume change caused by a deformation of the eye may also depend on the shape A myopic eye with an axis length larger than the diameter may at increasing compression of the

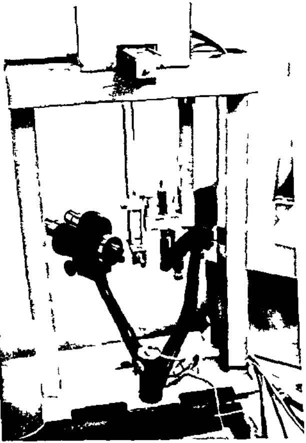


Fig 5a
The pressure chamber with adjacent arrangements The head support is removed *a* general view *b* detail of the pressure chamber

ageing The outer surface of the membrane is coated with a very thin layer of plastic (Seal Glo cold plastic) to avoid swelling in water No change in the properties of the membrane due to this coating is observed

The curvature of the membrane is estimated by measuring the position of the centre of the membrane in relation to the glass surface For this purpose a displacement transducer used (Hewlett Packard model 24 DCDT 050) which is placed within the metal b x The core of the transducer is connected to the centre of the membrane by a glass rod 0 9 mm in diameter glued to the rubber membrane centrally in the

The rubber membranes were kindly manufactured by Skega AB Ersmark Skellefteå Sweden

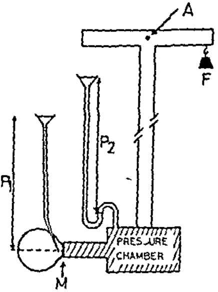


Fig 2

Schematic diagram of the apparatus A T shaped arm is movable around its axis (A) F represents an adjustable applanating force P_1 and P_2 represent adjustable pressures in the eye and in the pressure chamber respectively M indicates the membrane the curvature of the central part of which is recorded by a signal

suspended from a horisontal axis (*A* in Fig 2) The vertical bar of the T arm has a length of 36 cm *F* represents a known force obtained by an electro magnetic device acting on both ends of the horizontal bar The axis of the T arm is pivoted in bearings on a frame This is mounted on a *Haag Streit* slitlamp stand and thereby united with this instrument The apparatus is shown in Fig 3

The pressure chamber contains air the pressure of which is regulated by means of a water manometer The pressure is recorded by means of a transducer (Swema Sp 3100 D) Calibration is performed against the water manometer The pressure in the chamber and the applanating force are recorded continuously on a two channel strip chart recorder (Mosely 7100 BM)

A fixation point in the distance is obtained by use of a mirror in front of the eye not under examination The mirror reflects a fixation object (stripe pattern) at a distance of 2 metres

The pressure chamber shown in Fig 3b and in Fig 4 consists of a 2 5 cm long horizontal glass tube with an outer diameter of 10 mm and an aperture of 3 mm One of its ends is glued to a metal box (2 5 × 2 5 × 5 cm) The other end is ground down to a plane vertical surface which including its aperture is covered with a 40–60 μm thick transparent rubber membrane glued to the glass (M in Fig 2 4 and 5) The membrane is made of eten propen rubber (EPDM 1723–50) which has high resistance against

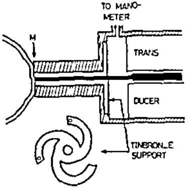


Fig 4

chematic d agram of the pressure chamber with transducer The thin membrane (M) overing the plane surface and the aperture is pressed against the cornea Dashed area epresents the walls of the pressure chamber Black area represents the glass rod and the core of the transducer

applanating force corresponding to 60 g A smaller deflection gives a correspondingly smaller force To avoid oscillations in the electromechanical system the time constant of the amplifier is adjusted to about 1 6 sec This means that after a shift of the mem brane signal caused by a deflection of 0 6 μm it takes 0 03 sec until a force shift of 1 g is produced and it takes 0 14 sec until a force shift of 5 g is produced A move ment sensitive transducer mounted at the T arm is connected to the amplifier in such a way that undue acceleration of the pressure chamber is avoided The delay caused by this is considered to be small

In all calibration experiments the applanating force is adjusted independent of the membrane signal

The position of the pressure chamber on the cornea is controlled through a facet cut on one side on the glass tube (Fig 5) Through the facet the applanated area and the aperture of the pressure chamber are observed by means of the microscope on the slitlamp stand To avoid distortion of the membrane signal by the weight of the glass rod and core of the transducer the pressure chamber must be kept horisontal Warning bulbs light up when the pressure chamber deviates 0 1 mm from the ideal position. The position of it is then if necessary manually adjusted by means of the equipment on the slitlamp stand

3 CALIBRATION ON ENUCLEATED EYES

In the calibration studies healthy human eyes removed post mortem within 24 hours were used

The relationship between the apparatus and an experimental eye appears in Fig ⁹ The enucleated eye was firmly fixed in a holder A 0 8 mm needle

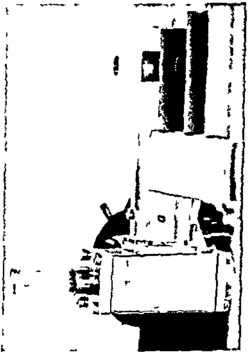


Fig 3b

aperture (Fig 4 and 5) The other end of the glass rod is suspended in the centre of a 0 07 mm thick support made of tinbronze (Cis 5428-07) and shown in Fig 4 in order to avoid friction in the pressure sensitive system The position of this tinbronze support can be slightly adjusted to locate the centre of the membrane as desired e g to correspond to a plane membrane when there is no pressure difference between the both sides of it At any position of the centre of the membrane the signal from the transducer can be zeroed (preset position) A change of the position then gives a new signal which is termed membrane signal indicating the degree of deflection from the preset position

The choice of the width of the aperture covered by the flexible membrane was governed by the following considerations Aperture diameters varying from 2–4 mm were tried A small diameter is advantageous because it permits a smaller applanated area to be investigated On the other hand the size of the membrane deflection decreases with decreasing diameter A diameter of 3 mm was used as a compromise

A constant current flowing through the electromagnetic device (represented in Fig 6 by the weight F) produces a force which is constant within a far greater range of movement of the arm than is used in experiments A signal from the current producing unit is recorded and calibrated against known weights The relationship between the signal and the produced force is linear and the signal is read with an accuracy corresponding to a weight of 0 2 g The friction of the mechanical parts causes a hysteresis of less than 0 1 g

The applanating force is controlled by the membrane signal by means of an amplifier A deflection of the center of the membrane of 0 6 μm from the preset position gives an

different values and the fourth was observed The calibration experiments were performed step by step and the variables were studied in the following order

Step 1 Adjustment of the preset position of the center of the membrane to correspond to a desired curvature of the membrane As mentioned above the preset position of the center of the membrane can be adjusted by means of the tinbronze support The deviation can also be maintained by a pressure dif ference between the eye and the pressure chamber In the experiments this deflection is always directed from the eye The degree of the deviation at the preset position is determined in relation to the plane reference surface by means of a flat calibration surface which is pressed against the membrane The mem brane can be made plane by increasing the pressure in the chamber i e it then coincides with the plane surface of the chamber the reference surface The membrane signal is used to calculate the distance between the preset position and the position corresponding to a plane membrane

Step 2 Adjustment of the pressure in the pressure chamber to a predeter mined level

Step 3 A predetermined small applanating force was applied to the pressure chamber The intraocular pressure was then adjusted in such a way that the membrane signal was zero i e the center of the membrane was in the preset position The applanating force was increased stepwise to predetermined values At each value the intraocular pressure resulting in a zero membrane signal was noted

With unchanged preset position (step 1) the pressure in the pressure chamber (step 2) was set at four different pressure levels corresponding to intraocular pressures of about 10 20 30 and 40 mmHg At each pressure level step 3 was carried out

Calibration Results

The results are presented as intraocular pressure plotted against applanated area at different values of preset position (step 1) and pressure in the pressure chamber (step 2) The applanated area is calculated according to the Imbert Fick law

With the preset position of the centre of the membrane corresponding to a plane membrane and a constant pressure in the pressure chamber of about 23 mmHg the intraocular pressure at different applanated areas varied according to Fig 6 From this figure it appears that the intraocular pressure is always

(Mediplast no 2) connected to an adjustable reservoir was pushed through the sclera at the insertion of the medical rectus muscle The tip of the needle was *placed in the centre of the pupil just in front of the anterior pole of the lens*

The size of the deflection of the center of the rubber membrane caused by a certain pressure change in one of the compartments depended mainly on the thickness and physical properties of the membrane and partly on the size of the applanated area With a pressure in both compartments of about 20 mmHg and a thickness of the rubber membrane of about 60 μm, the change in position caused by a pressure change in one of the compartments of 1 mmHg was about 1 μm at an applanated area of 15 mm², and about 1 5 μm at an applanated area of 40 mm²

The aim of the experiments delt with in the following part of this paper was to investigate the relationship between the intraocular pressure and the pressure in the pressure chamber and to study the influence of different preset positions of the center of the membrane The range of intraocular pressure to be studied was 10–40 mmHg (10 mmHg between each level) The smallest applanated area to be used in the clinical experiments was supposed to be about 20 mm Therefore 10–75 mm² was chosen as the range to be studied

Four variables could be observed The intraocular pressure the pressure in the pressure chamber the applanating force and the membrane signal

1) The intraocular pressure (represented by P_I in Fig 2) was maintained at a constant level by an open connection between the anterior chamber and the water reservoir The intraocular pressure was read in mm water

2) The pressure in the pressure chamber (represented by P in Fig 2) was obtained by a connection to an open water manometer and was read in mm water

All pressure values were converted into mmHg

3) The applanating force (represented by F in Fig 2) was measured by an electrical signal which was calibrated against known weights This signal was read with an accuracy corresponding to a weight of 0 2 g

4) The membrane signal was large enough to permit the reading of a pressure change in the eye or the pressure chamber of less than 2 mm water The accuracy was dependent on the thickness of the membrane When the applanating force the intraocular pressure and the pressure in the pressure chamber were kept constant there was a small signal drift which however was insignificant up to 15 minutes

To determine the relationship between the four variables in the experimental set up two of them were kept constant whereas the third variable was set at

different values and the fourth was observed The calibration experiments were performed step by step and the variables were studied in the following order

Step 1 Adjustment of the preset position of the center of the membrane to correspond to a desired curvature of the membrane As mentioned above the preset position of the center of the membrane can be adjusted by means of the tinbronze support The deviation can also be maintained by a pressure dif ference between the eye and the pressure chamber In the experiments this deflection is always directed from the eye The degree of the deviation at the preset position is determined in relation to the plane reference surface by means of a flat calibration surface which is pressed against the membrane The mem brane can be made plane by increasing the pressure in the chamber i e it then coincides with the plane surface of the chamber the reference surface The membrane signal is used to calculate the distance between the preset position and the position corresponding to a plane membrane

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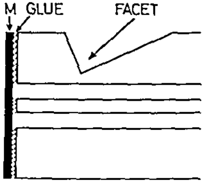


Fig 5

The tip of the pressure chamber The membrane (*M*) is glued to the glass surface and the glass rod The applanated area is observed through the facet

lower than the pressure in the pressure chamber and that the difference increases at smaller applanated areas The area of the aperture is about 7 mm and the smallest applanating surface used is about 10 mm to make sure that the applanation is caused not only by the movable membrane but also by the ground end of the glass tube

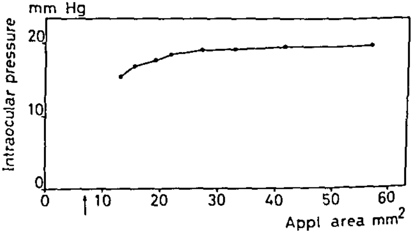


Fig 6

The intraocular pressure (ordinata) plotted against the calculated applanated area (abscissa) using constant pressure in the pressure chamber (about 23 mmHg) The applanated area is increased stepwise by increasing the applanating force At each step the intraocular pressure is adjusted to reset the plane membrane The applanated area is calculated according to applanating force/intraocular pressure Arrow indicates the area of the aperture of the pressure chamber

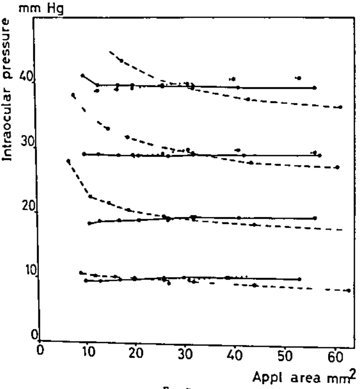


Fig 7

The effect of different degrees of concavity of the membrane on the pressure difference between the intraocular pressure and the pressure in the pressure chamber Using four levels of constant pressure in the pressure chamber the intraocular pressure (ordinata) resulting in a zero membrane signal is observed at different applanated areas (abscissa) At the preset positions used the deviation of the center of the membrane in relation to the reference surface was about

- •   • 30 μm
- •———• 60 μm
- •   • 90 μm

To overcome the disadvantages of varying difference between the intraocular pressure and the pressure in the pressure chamber experiments were carried out using a basic degree of concavity of the membrane Different preset positions were tried out in order to find an optimal preset position i e a position where the relationship between the intraocular pressure and the pressure in the pressure chamber was influenced as little as possible by the size of the ap planated area

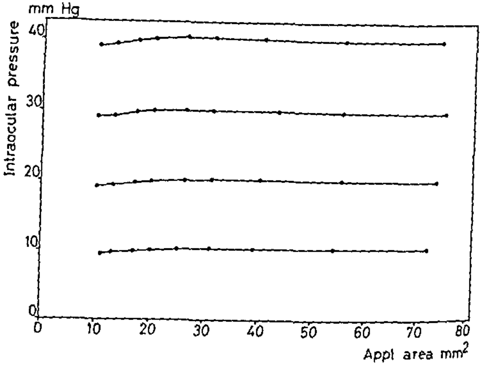


Fig 8

The mean of three observations of the intraocular pressure on each of nine eyes (ordinata) plotted against calculated applanated area (abscissa) The preset position used corresponded to a deviation of the center of the membrane of about 60 μm Using four levels of pressure in the pressure chamber (12.3, 22.3, 32.1 and 42.3 mmHg) the applanating force is increased stepwise At each step the intraocular pressure resulting in zero membrane signal is observed The applanated area is calculated according to applanating force/intraocular pressure

In the experiments the preset position (step 1 according to the procedure) was given three different values The deviation was maintained by a pressure difference between the eye and the pressure chamber At the preset positions used the deviation of the membrane's center was calculated to be about 30, 60 and 90 μm respectively At each step 1 step 2 was performed using four pressure levels At each step 2 step 3 was performed using eight values of applanating force As appears from Fig 7 the optimal preset position was found to be a deflection of the center of the membrane of about 60 μm in relation to the reference surface

To estimate the accuracy of the determination of the intraocular pressure repeated experiments with identical test programs were performed One and the same preset position was used at which the center of the membrane deviated about 60 μm in relation to the reference surface This was maintained by the

Table I

Results of three observations on each of nine eyes Procedure as in Fig 8 $P_{chamber}$ = pressure in the pressure chamber The mean (M) and the standard error of the mean (SE) of the observations of the intraocular pressure and the variances within each eye (S_W) and between the eyes (S_B) are given The right column shows the variances between eyes as a percentage of the total variance

$P_{chamber}$ mmHg	Applanating force g	Applanated area mm	*Intraocular pressure*				
			M mmHg	SE mmHg	S_W^2 mmHg	S_B^2 mmHg	$\frac{S_B \times 100}{S_W + S_B^2}$
12 5	1 35	11	9 4	0 28	0 14	0 64	83
12 5	1 75	13	9 7	0 21	0 13	0 34	74
12 5	2 25	17	9 9	0 20	0 06	0 34	85
12 5	2 7	20	10 0	0 20	0 06	0.33	85
12 5	3 5	25	10 2	0 18	0 06	0 29	83
1 5	4 25	31	10.3	0 19	0 07	0 31	81
12 5	5 5	39	10 3	0 19	0 05	0 37	86
12 5	7 5	54	10.3	0 19	0 04	0 32	88
1 5	10 0	72	10 3	0 16	0 03	0 20	85
2 5	2 7	10	19 2	0 41	0 66	1 29	66
22 5	3 5	13	19 4	0 32	0 33	0 78	70
22 5	4 5	17	19 7	0 28	0 26	0 63	71
22 5	5 4	0	19 9	0 26	0 20	0 53	73
2 5	7 0	26	20 1	0 24	0 13	0 48	79
2 5	8 5	31	20 2	0 21	0 11	0.37	77
2 5	11 0	40	20 2	0 21	0 07	0 39	85
2 5	15 0	55	20 0	0 19	0 05	0 32	85
2 5	0 0	74	19 9	0 16	0 05	0 19	9
3 1	4 05	10	29 1	0 55	0 6	2 43	76
3 1	5 25	13	29 2	0 38	0 44	1 17	73
3 1	6 75	17	29 8	0.34	0 7	0 96	78
3 1	8 1	20	30 0	0 33	0 16	0 95	86
3 1	10 5	26	30 1	0 29	0 09	0 72	88
3 1	1 8	31	30 1	0 2	0 08	0 60	89
3 1	17 5	43	30 0	0 24	0 06	0 47	89
3 1	0	55	29 8	0 21	0 0	0.39	59
3 1	30 0	75	29	0 17	0 04	0 22	83
4 3	5 4	10	39 1	0 66	0 29	3 90	93
4 3	0	13	39 3	0 46	0 13	1 84	94
4 3	9 0	1	39 9	0 41	0 11	1 42	93
42 3	10 8	0	40 2	0 3	0 10	1 17	92
4 3	14 0	26	40 4	0 3	0 10	0 88	90
4 3	1 0	31	40 4	0 29	0 08	0 71	90
4 3	0	40	40 2	0 25	0 08	0 54	87
4 3	30 0	5	40 0	0 22	0 07	0 44	87
42 3	40 0	4	39 9	0 18	0 0	0 26	83

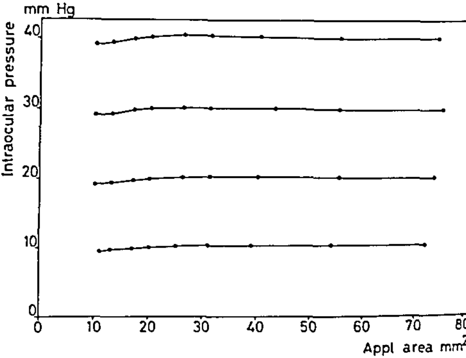


Fig 8

The mean of three observations of the intraocular pressure on each of nine eyes (or dinata) plotted against calculated applanated area (abscissa) The preset position used corresponded to a deviation of the center of the membrane of about 60 μm Using four levels of pressure in the pressure chamber (12 3 22 3 32 1 and 42 3 mmHg) the ap planating force is increased stepwise At each step the intraocular pressure resulting in zero membrane signal is observed The applanated area is calculated according to applanating force intraocular pressure

In the experiments the preset position (step 1 according to the procedure) was given three different values The deviation was maintained by a pressure difference between the eye and the pressure chamber At the preset positions used the deviation of the membrane s center was calculated to be about 30 60 and 90 μm respectively At each step 1 step 2 was performed using four pres sure levels At each step 2 step 3 was performed using eight values of ap planating force As appears from Fig 7 the optimal preset position was found to be a deflection of the center of the membrane of about 60 μm in relation to the reference surface

To estimate the accuracy of the determination of the intraocular pressure repeated experiments with identical test programs were performed One and the same preset position was used at which the center of the membrane deviated about 60 μm in relation to the reference surface This was maintained by the

Table 1

Results of three observations on each of nine eyes Procedure as in Fig 8 P_{chamb} = pressure in the pressure chamber The mean (M) and the standard error of the mean (SE) of the observations of the intraocular pressure and the variances within each eye (S_W) and between the eyes (S_B^2) are given The right column shows the variances between eyes as a percentage of the total variance

P_{chamb} mmHg	Applanating force g	Applanated area mm	Intraocular pressure				
			M mmHg	SE mmHg	S_W mmHg	S_B^2 mmHg	$\frac{S_B \times 100}{S_W^2 + S_B}$
12 3	1 35	11	9 4	0 28	0 14	0 64	83
12 3	1 75	13	9 7	0 21	0 13	0 34	74
12 3	2 25	17	9 9	0 20	0 06	0 34	85
12 3	2 7	20	10 0	0 20	0 06	0 33	85
12 3	3 5	25	10.2	0 18	0 06	0 29	83
12 3	4 2	31	10 3	0 19	0 07	0 31	81
12 3	5 5	39	10 3	0 19	0 05	0 32	86
12 3	7 5	54	10.3	0 19	0 04	0 32	88
12 3	10 0	72	10 3	0 16	0 03	0 20	85
22 3	2 7	10	19 2	0 41	0 66	1 29	66
22 3	3 5	13	19 4	0 32	0 33	0 78	70
22 3	4 5	17	19 7	0 28	0 26	0 63	71
22 3	5 4	20	19 9	0 26	0 20	0 53	73
22 3	7 0	26	20 1	0 24	0 13	0 45	79
[illegible] 3	8 5	31	20 2	0 21	0 11	0.37	77
[illegible] 3	11 0	40	20 2	0 21	0 07	0 39	85
[illegible] 3	15 0	55	20 0	0 19	0 05	0 32	85
[illegible] 3	[illegible]0 0	74	19 9	0 16	0 05	0 19	79
3[illegible] 1	4 05	10	29 1	0 55	0 76	2 43	76
3[illegible] 1	5 2	13	29 2	0 38	0 44	1 17	73
32 1	6 75	17	29 8	0.34	0 27	0 96	8
32 1	8 1	[illegible]0	30 0	0 33	0 16	0 95	86
3[illegible] 1	10 5	26	30 1	0 29	0 09	0 [illegible]	88
32 1	1[illegible] 8	31	30 1	0 27	0 08	0 60	89
3[illegible] 1	1[illegible] 5	43	30 0	0 24	0 06	0 47	89
3[illegible] 1	[illegible]0	55	29 8	0 21	0 05	0 39	89
3[illegible] 1	30 0	[illegible]	29 [illegible]	0 1[illegible]	0 04	0 2[illegible]	83
4[illegible] 3	5 4	10	39 1	0 66	0 29	3 90	93
42 3	7 0	13	39 3	0 46	0 13	1 84	94
4[illegible] 3	9 0	1[illegible]	39 9	0 41	0 11	1 42	93
4[illegible] 3	10 8	[illegible]0	40 2	0 3	0 10	1 17	9
42 3	14 0	[illegible]6	40 4	0 3	0 10	0 88	90
4[illegible] 3	1[illegible] 0	31	40 4	0 29	0 08	0 [illegible]1	90
4[illegible] 3	[illegible]0	40	40 2	0 25	0 08	0.54	87
4[illegible] 3	30 0	55	40 0	0 2	0 0	0 44	87
4[illegible] 3	40 0	[illegible]4	39 9	0 18	0 05	0 26	83

tinbronze support The pressure in the pressure chamber (step 2 in the procedure) was set at four different levels 12.3 22.3 32.1 and 42.3 mmHg These values were chosen because 2.3 mmHg seemed to be a remaining pressure difference between the intraocular pressure and the pressure in the chamber at this preset position The applanating force (step 3 in the procedure) was given nine values at each step 2 When step 2 was performed i e the four pressure levels were studied with step 3 step 2 was started again The program was run from the beginning three times on nine eyes

The results are presented as follows At each pressure level in the pressure chamber the mean and the standard error of the mean of the intraocular pressures at each force value and the variances within and between eyes were calculated(9) The applanated area was calculated according to the Imbert Fick law from the mean value of the intraocular pressure and the applanating force The results are presented in Fig 8 where the mean values of the intraocular pressure are plotted against the calculated applanated area In Table I are presented the mean values of the intraocular pressure together with the standard error of the mean and the variances The variances both within and between eyes decreased with increasing size of the applanated area The variance between eyes was always much larger than the variance within eyes and accounted as a rule for 80 % of the total variance

Discussion of the Calibration Results

The experiments described above have shown a nearly constant relationship between the intraocular pressure and the pressure in the pressure chamber This is independent of the size of the applanated area within the limits of 20–75 mm The optimum curve of the membrane was then concave with the center of the membrane deviating towards the pressure chamber about 60 μm in relation to the reference surface Under these conditions an average pressure difference between the pressure in the pressure chamber and the intraocular pressure of about 2 mmHg remained and the intraocular pressure was always the lower one The reason for this pressure difference may be taken as effects of the cornea s resistance to deformation and of the surface tension (c f page 2) The intraocular pressures observed within the pressure range investigated (10–40 mmHg) showed a comparatively small variance within one and the same enucleated eye The variance between different eyes was considerably larger

The fact that supposedly similar enucleated eyes differed in these calibration experiments is a matter of interest The results indicate that different corneas

have different physical properties This is compatible with the experiments concerning the validity of the Imbert Fick law discussed above (page 3) When the variation between eyes is great not very much can be gained by further increasing the accuracy of the determination of the intraocular pressure in the single eye Since the variation between the eyes is considerable in the present statistics it might be anticipated that the variation is at least the same under dynamic living conditions

Due to the slight concavity of the central part of the pressu e chamber tip there was not a strictly plane applanation However the word applanation will continue to be used with this reservation in mind as the deviation from a plane surface is very small The partial flattening of the cornea by the mem brane covering the aperture of the pressure chamber (diameter 3 mm) with a concavity corresponding to the optimum preset position results in a difference of the displaced volume of 0 3 μl compared with that obtained by applanation using a plane surface This is systematically induced error which is disregarded The concavity of the part of the membrane covering the aperture will in principle neither affect the applanating force nor the calculation of the ap planated area as long as this area is larger than the area of the aperture

The degree of deflection of the membrane was to some extent depending on the size of the applanated area (page 9) The reason for this slight dependency is not clear However this is of limited importance as the center of the membrane is always reset to the preset position The influence of the varying deflection only affect the steepness of the servo system

Primarily the aim of the apparatus is not to be an instrument for accurate determination of the intraocular pressure but to achieve an applanating force that varies in such a way as to keep the intraocular pressure constant during an experiment The results obtained indicate that the apparatus is capable of keeping the intraocular pressure constant within very close limits probably within tenths of mmHg At the same time it makes is possible to estimate the intraocular pressure with an accuracy which is regarded as sufficient

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ON THE OSCILLATORY POTENTIALS OF THE HUMAN ELECTRORETINOGRAM IN LIGHT AND DARK ADAPTATION

I. Thresholds and relation to stimulus intensity on adaptation to short flashes of light. A Fourier analysis

BY

P. ALGVERE, L. WACHTMEISTER and S. WESTBECK

The oscillatory potentials of the human ERG were studied in response to a series of three short light flashes of high luminance, the first two flashes conditioning a varying light adaptation of the retina. The energy and dominant frequency of the oscillatory response were evaluated mathematically by a combined impulse response and Fourier analysis.
Most prominent oscillations were elicited when the retina was light adapted by strong conditioning flashes and stimulated at intervals of 30 sec or 1 min. The maximal intensity of stimulus light (log I = 0) was about × 10⁴ photopic candelas/m². The scotopic b wave was evoked at threshold by a stimulus intensity of log I = −6.0. A distinct photopic b wave was recorded at log I = −4.0 and the a wave at log I = −3.3. Traces of oscillatory potentials were found at log I = −3.3 and log I = −3.0 in different experiments, thus approximately at the same intensity as the a wave. There was a linear increase of the energy of the oscillatory potentials on augmentation of stimulus intensity over three log units. Peak latencies of oscillatory potentials showed a fairly uniform shortening (about 6 msec) on increasing stimulus intensity provided that the retinal light adaptation was kept constant, and the dominant frequency of the oscillatory response remained within 110–130 Hz. When the retinal adap-

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tation to light was increased by stronger conditioning flashes peak latencies for the first and second oscillatory peak diminished those for the third and fourth peak showing no significant change Then the dominant frequency of the oscillations declined from about 155 Hz (in dark adaptation) to about 110 Hz (in light adaptation) It was found that the peak latencies of the oscillatory potentials are defined by the stimulus intensity but the frequency of this response varies with the state of retinal neural adaptation caused by short flashes of light

Key words electroretinography – oscillatory potentials – light and dark adaptation – Fourier analysis – thresholds – relation to stimulus intensity – high intensity flashes

To elicit the oscillatory potentials of the human electroretinogram (ERG) a light stimulation of high intensity has frequently been used (Cobb & Morton 1953 Bornschein & Goodman 1957 Yonemura Tsuzuki & Aoki 1962 Genest 1964 Tassy 1966 Algvere 1967 and many others) By means of a slowly flickering light of moderate intensity distinct oscillations can also be evoked (Heck & Rendahl 1957 Auerbach 1962) A certain adaptation to light caused by short flashes seems to facilitate the regeneration of retinal oscillatory potentials It has been demonstrated that these oscillations gain in amplitude when the comparatively fast neural phase of retinal adaptation is prevailing (Algvere & Westbeck 1972)

It has long been known that an increase in stimulus intensity is accompanied by a gain in amplitude of the electric retinal response (Dewar & McKendrick 1873 Einthoven & Jolly 1908) There exists a wide range of intensities over which logarithmic increments in stimulus produce constant steps of increase in amplitude of the ERG For example this has been shown for the scotopic b wave of human ERG (Karpe 1945 Riggs Berry & Wayner 1949 Johnson & Riggs 1951 Armington 1953 Johnson & Bartlett 1956) as well as for the a wave (Armington Johnson & Riggs 1952 Bornschein & Goodman 1957) As in other approximations to Weber s law the generalization fails at the extremes

Little is known of the light stimulus necessary for eliciting the oscillatory potentials at threshold The knowledge of the relation between stimulation intensity and amplitude of the oscillatory potentials is likewise limited It has been stated that the oscillatory potentials are augmented with an increase of light stimulus intensity (Yonemura Tsuzuki & Aoki 1962 Tsuchida Kawasaki & Jacobson 1971) The time intervals between the stimulating flashes are however of decisive importance on the result If this interval is short enough there remains a considerable retinal adaptation to light at that point of time when

consecutive flashes are given and the oscillatory potentials are recorded modified in shape and size

With increasing stimulation intensity a shortening of the time course of ERG occurs (Granit 1947 Bornschein Goodman & Gunkel 1957) Regarding the oscillatory potentials Bornschein & Goodman (1957) observed the peak latency (implicit time) for each individual oscillatory peak to decrease with augmentation of stimulus intensity However Auerbach (1967) considered these latencies to remain practically independent of stimulation intensity The frequency of oscillations was reported to be around 140 Hz (Bornschein & Goodman 1957) and unaltered despite the fact that stimulus intensity was varied (Yonemura Tsuzuki & Aoki 1962) The evaluation of the frequency is however complicated by the fact that the oscillatory peaks are not always separated by constant time intervals as observed in the human ERG (Genest 1964) and in that of the pigeon (Nye 1968)

In recent studies the dominant frequency of oscillatory potentials of human ERG was found to change from 120–130 Hz in light adaptation towards 160 Hz in dark adaptation (Algvere & Westbeck 1972) The aim of the present work was to study the oscillatory potentials of the human ERG after adaptation to short flashes of light and then in response to varying stimulus intensity A mathematical evaluation of the amplitude and frequency of oscillatory potentials was enabled by a combined impulse response and Fourier analysis

Apparatus and Methods

Apparatus

The apparatus for recording the ERG was the same as that previously described (Algvere 1968) The light stimulus was delivered by an electronic flash (Braun F 80 *professional*) which was mounted on the top of a lamp housing specially constructed for electroretinography (Karpe & Algvere 1967) The lamp screen was placed 20 cm in front of the subject s eye providing uniform illumination under a visual angle of about 110 The colour temperature of the stimulus light corresponded to about 6500 K The maximum luminance of the light stimulus was about 5×10^4 photopic candelas/m and could be reduced in a logarithmic scale by neutral density filters

The luminance flux from the electronic flash attained maximum in less than msec and was then reduced along an exponential curve 5% of the luminance intensity was maintained for only about 2 5 msec (0 9 msec to 3 4 msec from the onset of light stimulus) The electric potentials from the eye were led off with

a contact lens electrode (Lawwill & Burian 1966) The reference electrode was a part of the contact lens and orientated to the inside of the lower eye lid The ground electrode was placed on the ear lobe The signal was amplified using a preamplifier with differential input and displayed on a double beam cathode ray oscilloscope (Solartron CX 1442 3) The ERG was presented on one cathode ray beam with the timing of light stimulus on the other The display was photographed with a Polaroid I and camera without reduction in size The camera shutter triggered the oscilloscope The electronic flash was delayed 5–10 msec after the oscilloscope sweep started The calibration deflection used for recording the oscillatory potentials was 0 1 mV–10 msec/cm and was set to 0 2 mV–20 msec/cm or 0 1 mV–20 msec/cm when recording slower potentials (a and b waves)

The bandpass of the recording system (3 db points) was about 3–25 000 Hz the frequency response being flat from about 80–5000 Hz enabling the oscillatory potentials which have a frequency of about 100–160 Hz to be adequately recorded When recording the slower components (a and b waves) the frequency response was unfiltered and flat from about 15–11 000 Hz No active filter was used

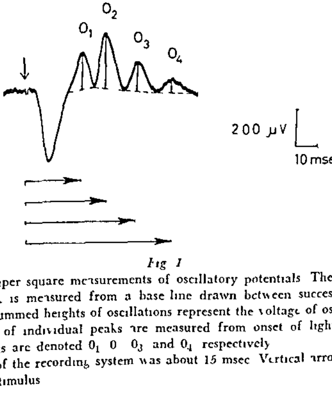


Fig 1

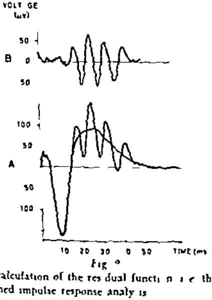
Method of calliper square measurements of oscillatory potentials The height of each oscillatory peak is measured from a base line drawn between successive troughs of wavelets The summed heights of oscillations represent the voltage of oscillatory potentials Latencies of individual peaks are measured from onset of light stimulus The oscillatory peaks are denoted O_1 O_2 O_3 and O_4 respectively

Time constant of the recording system was about 15 msec Vertical arrow indicates the onset of light stimulus

Methods of measurement

Peak latencies and the amplitude of the a wave and the b wave (measured from the base line) were evaluated by calliper square measurements To estimate the amplitude of the oscillatory potentials the heights of the wavelets were measured by means of a measuring magnifier according to the method illustrated in Fig 1 The sum of the heights of wavelets was then calculated This simple estimation of the oscillatory potentials is however afflicted with certain sources of error There is an interference between the oscillations and slower components (a and b waves) the shape and size of the latter influencing the appearance of the former

To get more accurate estimates of the oscillatory potentials a mathematical evaluation of the ERG curves was performed using a combined impulse response and Fourier analysis (see Algvere & Westbeck 1972) The ERG was regarded as consisting of a biphasic slow response (a and b waves) with superimposed oscillations The oscillatory potentials were isolated from the



Fig

Method I computer calculation of the res dual functi n i e the oscillatory potentials by means of a combined impulse response analy is

A T tal ERG an} the curve approximat ng the biphasic slow resp nse (a and b waves)

B Isolated oscillatory potentials inclu ling base l ne noise as the residual function after subtract on of the approximating curve (shown in A) from the total ERG

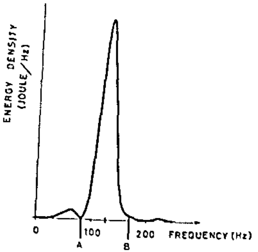


Fig 3
Energy density spectrum of oscillatory potentials according to a Fourier analysis The energy attributable to oscillatory potentials is the energy underlying the maximum energy peak in a certain frequency range indicated by A and B Linear scale on y axis

total ERG curve and the residual functions obtained were studied separately by Fourier transforms (Fig 2)

By means of a curve tracer and an analog digital converter (Department of Plasma Physics Royal Institute of Technology Stockholm) the ERGs were digitized Then use was made of an impulse response analysing program developed at the Department of Telecommunication Theory Royal Institute of Technology Stockholm expressed in the programming language Algol and adapted to the computer IBM 360 (Westbeck 1971)

The energy and frequency attributable to the oscillations is illustrated in an energy density spectrum (Fig 3) The energy of the oscillatory potentials is obtained by integration of the area underlying the maximal energy density peak The dominant frequency is indicated by the maximal peak of the energy density spectrum in the range in question

Procedures

Investigations were made on four young and healthy persons – two women and two men Surface anaesthesia of the eye was induced with a few drops of Novesin® (Wander) Maximal mydriasis was established by Mydriacyl® (Alcon lab) the diameter of the eye pupil being expanded to more than 6 mm The fellow eye was occluded

The subjects were dark adapted for 30 min The first ERG s recorded showed whether the intended dark adaptation had been achieved A flash of maximal intensity then caused a light adaptation that persisted until the next flash (30 seconds later) struck the eye At that point of time the adaptometric visual threshold was found to be somewhat below 6×10^{-5} lux (Algvere 1967)

The ERG s shown in the following pictures are all recorded from the left eye of the same subject and evaluated by calliper square and magnifier measurements as well as by Fourier analysis

The visual acuity visual fields adaptometric visual sensitivity and colour sense were normal

The following two procedures were performed

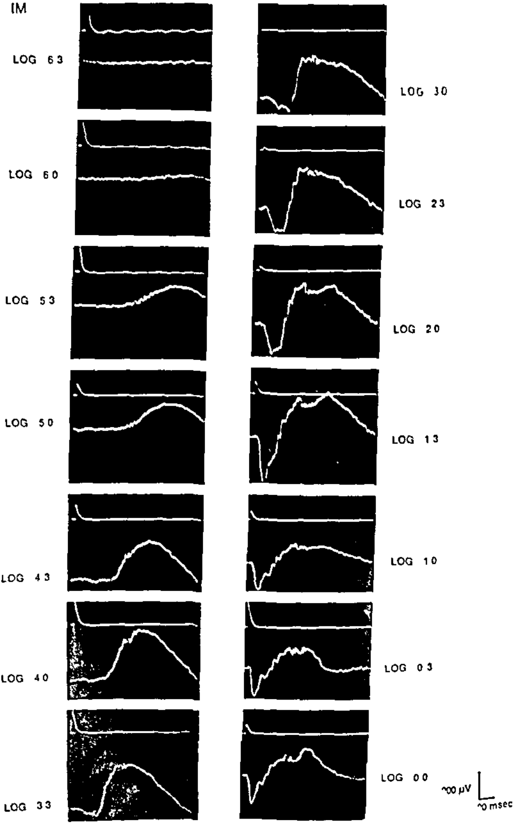
I After dark adaptation for 30 minutes the ERG threshold was studied The light stimulus was succeedingly increased from a weak intensity ($\log I_s = -10$) with steps of one log unit or less up to full intensity ($\log I_s = 0$) The interval between each flash was 30 sec or 1 min for the weak stimuli (up to $\log I = -3\,3$) and after that the interval was prolonged to 5 min or more for the strong stimuli

To study the threshold of the oscillatory potentials series of three flashes with 30 sec intervals between stimuli were given and the ERG in response to the third (stimulus) flash was studied The first two flashes induced a particular adaptation to light and will be referred to as conditioning flashes

In one experiment the intensity of the two conditioning flashes was equal to that of the third Succeedingly the intensity of the three flashes in each series was increased in logarithmic scale over a range of 5 log units The interval between each series of three flashes was 5 min

In another experiment the two conditioning flashes were of constant and maximal intensity ($\log I = 0$) Then the intensity of the third flash was likewise varied over a range of 5 log units The interval between each series of three flashes was 30 sec The latter procedure was also used for evaluating the effect of the two conditioning flashes on the a wave recorded in response to the third flash

II The dependence of the oscillatory potentials on the light stimulus intensity was studied in response to the last flash in a series of three The stimulation intensity was varied over 5 log units Two types of conditioning flashes were used as in the previous procedures for measuring the thresholds



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LOG 3 0
LOG 2 3
LOG 2 0
LOG 1 3
LOG 1 0
LOG 0 3
LOG 0 0
msec

Results

I ERG THRESHOLDS

The ERG was recorded after a dark adaptation of 30 min The interval between the flashes was set to 30 sec or 1 min for the weak stimuli and was prolonged to 5 min or more for the strong stimuli

Traces of a scotopic b wave were elicited by a stimulus intensity of around log I = -8 0 On repetitive light stimulation with intervals of 5 min between the flashes a scotopic b wave of about 20 μV was not recorded until the intensity of stimulus light was log I = -6 0 The peak latency of the b wave elicited was measured to be about 120 msec (Fig 4)

A photopic b wave appeared at a stimulus intensity of log I = -4 0 and had a peak latency of about 60 msec (Fig 4) This implicit time was consistent with the observations of Jacobson Hirose & Popkin (1967)

An a wave of about 50 μV amplitude was elicited by a stimulus intensity of log I = -3 3 and had a dual appearance in response to that stimulus The peak latency was about 30 msec for the second negative peak this being the largest At a higher stimulation intensity (log I_s = -2 0) the peak latency was shortened to about 15 msec for the first negative peak which was then the largest (Fig 4) At maximal stimulus intensity the peak latency of the a wave became about 8 msec

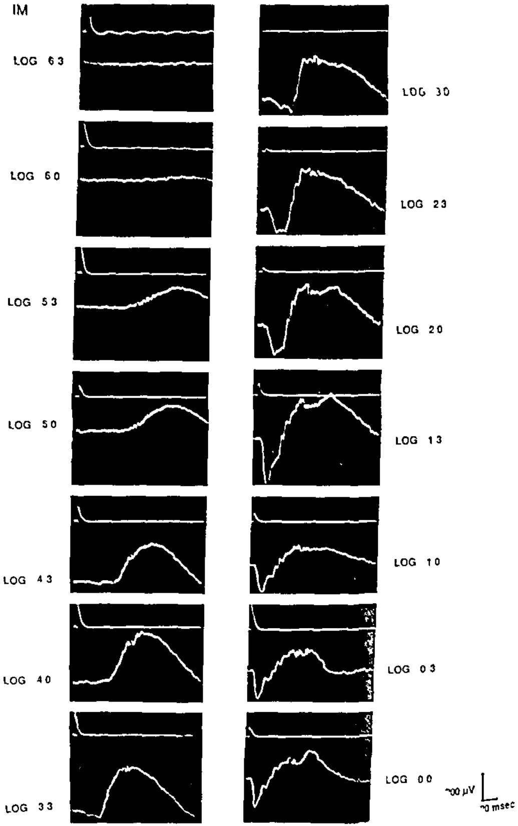
In dark adaptation the threshold of the a wave was studied after two conditioning flashes of maximal intensity (log I_c = 0) in response to a third (stimulus) flash As in the above procedure the threshold of the a wave was found at a stimulus intensity of log I = -3 0 Consequently the conditioning light adaptation of the retina to previous flashes did not alter the a wave threshold significantly

To study the duration of the light adapting effect of previous flashes on the oscillatory potentials two experiments were performed in dark adaptation. In one experiment the interval between the two conditioning flashes and the third stimulus flash was varied between 5 min and 15 sec the interval being

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Fig 4

ERGs recorded after dark adaptation for 30 min showing a and b waves at threshold Maximal intensity of light stimulus was 5 × 10³ photopic candelas m (log I = 0) On repetitive light stimulation every five minutes a scotopic b wave of 20 μV was recorded in response to a light stimulus of log I = -6 0 At log I = -3 3 the a wave became visible Photopic b wave appeared at an intensity of log I = -4 0 In the last three records (log I = -1 0 to 0) the vertical calibration represents 400 μV Time constant of the recording system was about 300 msec Upper cathode ray beam indicates onset of light stimulus


IM
LOG 6 3
LOG 6 0
LOG 5 3
LOG 5 0
LOG 4 3
LOG 4 0
LOG 3 3
LOG 3 0
LOG 2 3
LOG 2 0
LOG 1 3
LOG 1 0
LOG 0 3
LOG 0 0
msec

Results

I ERG THRESHOLDS

The ERG was recorded after a dark adaptation of 30 min The interval between the flashes was set to 30 sec or 1 min for the weak stimuli and was prolonged to 5 min or more for the strong stimuli

Traces of a scotopic b wave were elicited by a stimulus intensity of around log I_s = −8 0 On repetitive light stimulation with intervals of 5 min between the flashes a scotopic b wave of about 20 μV was not recorded until the intensity of stimulus light was log I = −6 0 The peak latency of the b wave elicited was measured to be about 120 msec (Fig 4)

A photopic b wave appeared at a stimulus intensity of log I_s = −4 0 and had a peak latency of about 60 msec (Fig 4) This implicit time was consistent with the observations of Jacobson Hirose & Popkin (1967)

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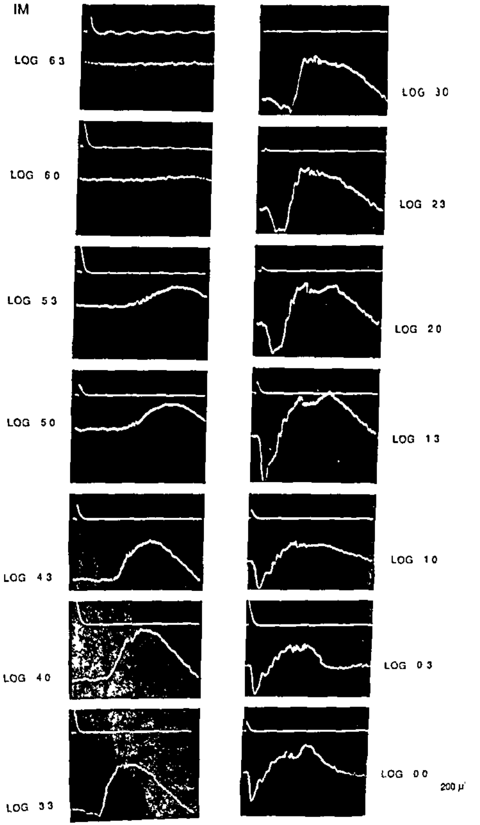
In dark adaptation the threshold of the a wave was studied after two conditioning flashes of maximal intensity (log I_c = 0) in response to a third (stimulus) flash As in the above procedure the threshold of the a wave was found at a stimulus intensity of log I = −3 0 Consequently the conditioning light adaptation of the retina to previous flashes did not alter the a wave threshold significantly

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Fig 4

ERG s recorded after dark adaptation for 30 min show ng a and b waves at threshold Maximal intensity of light st mulus was 5 × 10⁴ photopic candelas/m (log I = 0) On repetitive light stimulation every five minutes a scotopic b wave of 20 μV was reco ded in response to a l ght st mulus of log I = −6 0 At log I_s = −3.3 the a wave became visible Photop c b wave appeared at an intens ty of log I = −4 0 In the last three records (log I = −1 0 to 0) the vert cal cal bration represents 400 μV T me c nstant of the recording system was about 300 msec Upper cathode ray beam ndicates onset f light stimulus


IM
LOG 6 3
LOG 6 0
LOG 5 3
LOG 5 0
LOG 4 3
LOG 4 0
LOG 3 3
LOG 3 0
LOG 2 3
LOG 2 0
LOG 1 3
LOG 1 0
LOG 0 3
LOG 0 0
200 μ'

Results

I ERG THRESHOLDS

The ERG was recorded after a dark adaptation of 30 min. The interval between the flashes was set to 30 sec or 1 min for the weak stimuli and was prolonged to 5 min or more for the strong stimuli.

Traces of a scotopic b wave were elicited by a stimulus intensity of around log $I_s = -8.0$. On repetitive light stimulation with intervals of 5 min between the flashes a scotopic b wave of about 20 μV was not recorded until the intensity of stimulus light was log $I_s = -6.0$. The peak latency of the b wave elicited was measured to be about 120 msec (Fig. 4).

A photopic b wave appeared at a stimulus intensity of log $I = -4.0$ and had a peak latency of about 60 msec (Fig. 4). This implicit time was consistent with the observations of Jacobson, Hirose & Popkin (196?).

An a wave of about 50 μV amplitude was elicited by a stimulus intensity of log $I = -3.3$ and had a dual appearance in response to that stimulus. The peak latency was about 30 msec for the second negative peak, this being the largest. At a higher stimulation intensity (log $I_s = -2.0$) the peak latency was shortened to about 15 msec for the first negative peak which was then the largest (Fig. 4). At maximal stimulus intensity the peak latency of the a wave became about 8 msec.

In dark adaptation the threshold of the a wave was studied after two conditioning flashes of maximal intensity (log $I = 0$) in response to a third (stimulus) flash. As in the above procedure the threshold of the a wave was found at a stimulus intensity of log $I = -3.0$. Consequently the conditioning light adaptation of the retina to previous flashes did not alter the a wave threshold significantly.

To study the duration of the light adapting effect of previous flashes on the oscillatory potentials two experiments were performed in dark adaptation. In one experiment the interval between the two conditioning flashes and the third stimulus flash was varied between 5 min and 15 sec, the interval being

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Fig. 4

ERGs recorded after dark adaptation for 30 min showing a and b waves at threshold. Maximal intensity of light stimulus was 5×10^4 photopic candelas/m (log $I = 0$). On repetitive light stimulation every five minutes a scotopic b wave of ?0 μV was recorded in response to a light stimulus of log $I = -6.0$. At log $I_s = -3.3$ the a wave became visible. Photopic b wave appeared at an intensity of log $I = -4.0$. In the last three records (log $I = -1.0$ to 0) the vertical calibration represents 400 μV. Time constant of the recording system was about 300 msec. Upper cathode ray beam indicates onset of light stimulus.

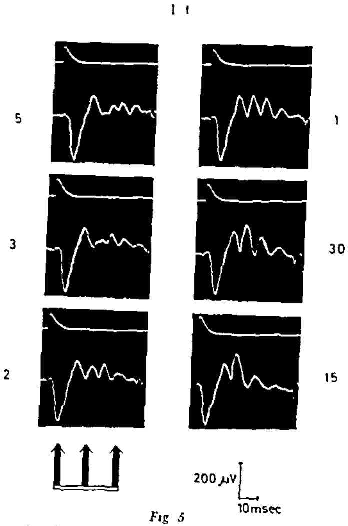


Fig 5

Oscillatory potentials of ERG recorded in dark adaptation evoked by stimuli of constant intensity (log I = 0) and at varying intervals between the flashes (denoted by minutes and seconds) Most prominent oscillatory potentials were recorded at intervals of 1 minute or 30 seconds The ERG in response to the third flash in a series is shown in each picture
Stimulation pattern is symbolized by vertical arrows (flashes) connected by horizontal bar (time interval between flashes) Black symbol denotes a constant condition white symbol is a variable

succeedingly shortened during the experiment The stimulus light used was of constant and maximal intensity (log $I_s = 0$) Most prominent oscillations were recorded at an interval of either 1 min or 30 sec between the flashes (Fig 5) This result is consistent with earlier observations the energy of the oscillatory response being recorded maximal at this stimulation interval (Algvere & Westbeck 1972)

In another experiment an evaluation of the effect of the intensity of previous conditioning flashes on the oscillatory response was sought The intensity of the conditioning flashes was varied over 10 log units The third (stimulus) flash was of constant and maximal intensity In order to let the retina recover from

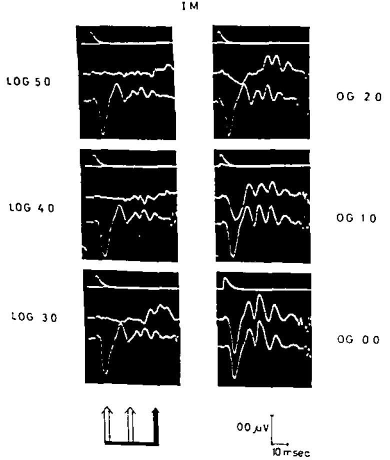


Fig 6

Oscillatory potentials after conditioning light adaptation from flashes of different intensity ERG s were recorded in darkness at an interval of 30 seconds between each flash and 5 minutes between each series of flashes The intensity of two conditioning flashes was succeedingly increased and the third (stimulus) flash was set at maximal inten ity (log I = 0) Most prominent oscillations appeared with strong conditioning flashes (log I = -1 0 and 0) Each picture shows the ERG in response to the second condit on ng and the third (stimulus) flash Symbols of stimulation pattern as in Fig 5

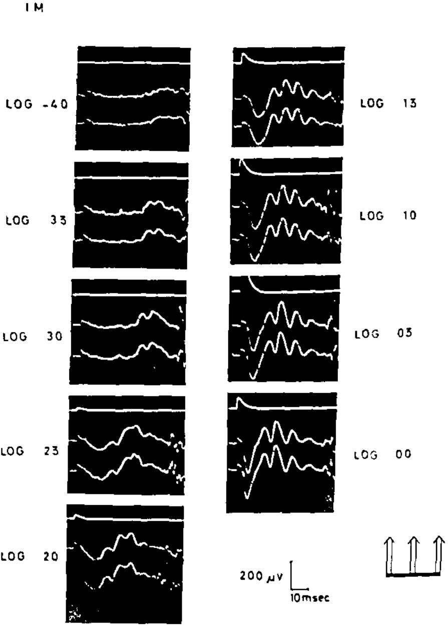


Fig. 7

Oscillatory potentials recorded after adaptation to two (conditioning) flashes of the same intensity as the third (stimulus) flash. The intensity of all three flashes was succeedingly increased from log −5 to log 0. The interval between the three flashes in each series was 30 seconds and five minutes elapsed before a following series of stronger flashes was given. Symbols of stimulation pattern as in Fig. 5.
The oscillatory potentials first appeared at a stimulation intensity of log $I_s = -3.3$.
Each picture shows the ERG in response to the second conditioning flash and the (third) stimulus flash.

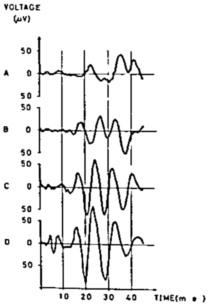


Fig 8

Oscillatory potentials as residual function including base line noise isolated from the ERGs shown in Fig 7 The stimulus intensity was log I = −3 0 (A) log I = −?0 (B) log I = −1 0 (C) and log I_s = 0 (D) respectively The frequency of the oscillatory potentials decreased from about 155 Hz to 110 Hz

light adapting effects caused by previous stimulation the interval between each series of three flashes was set to 5 min The oscillatory potentials were recorded most prominent when the two conditioning flashes were of high intensity (log I_c = −1 0 or log 0) (Fig 6)

Evidently the most appropriate light adaptation for eliciting the oscillatory potentials was achieved by a stimulation interval of 30 sec when conditioning flashes of highest intensity available were used This stimulation interval was kept constant when evoking oscillations in the following experiments

To study the threshold of the oscillatory potentials three consecutive flashes were given at an interval of 30 sec and the ERG in response to the third flash was evaluated The two conditioning flashes and the third ((stimulus) flash were of the same intensity which was varied for all three over 5 log units The oscillatory potentials appeared at a stimulation intensity of log I = −3 3 (Fig 7)

The threshold of the oscillations was also studied after two conditioning

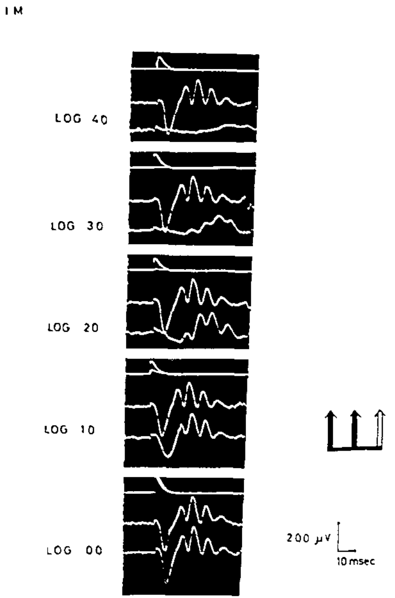


Fig 9

Oscillatory potentials after adaptation to two (conditioning) flashes of constant and maximal intensity (log $I_c = 0$) and in response to a third (stimulus) flash of varied intensity The intensity of the latter was changed from log − 5 to log 0
The flashes were given every 30 sec throughout this experiment Oscillatory potentials first appeared at a stimulation intensity of log $I_s = -3\ 0$ Each picture shows the ERG in response to the second conditioning flash and the third (stimulus) flash Symbols of stimulation pattern as in Fig 5

flashes at maximal intensity (log $I_c = 0$) and in response to a third (stimulus) flash The intensity of the latter was varied and thereby increased by steps of one lo unit The oscillatory potentials appeared then at a stimulation intensity of lo_g $I_s = -3\ 0$ (Fig 9)

II RELATIONS TO STIMULUS INTENSITY

To study the dependence of oscillatory potentials on the stimulation intensity three consecutive flashes were given at an interval of 30 sec and the ERG recorded in response to the third (stimulus) flash

In one experiment the two conditioning flashes were of constant and maximal intensity and only the intensity of the third (stimulus) flash was varied (over 5 log units) The energy of the oscillatory potentials was found to in crease linearly with augmentation of light stimulus intensity over a range of

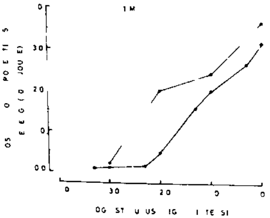


Fig 10

Calculated energy of oscillatory potentials in relation to stimulus intensity The energy was calculated as illustrated in Fig 5 and plotted against log stimulus light intensity of the third (stimulus) flash eliciting the ERG s shown in Figs 7 and 9
Black c rcl s The two conditioning flashes were of constant and maximal intensity and the lum nance of the th rd (stimulus) flash was succeedingly increased
Open i cle The conditioning flashes and the third (stimulus) flash were of the same intensity wh ch for all three flashes was succeedingly increased At weak stimulation (log I = −5.3 to −° 3) the oscillatory energy was low and unaltered At higher sti mulation intensities there was a linear increase of the energy

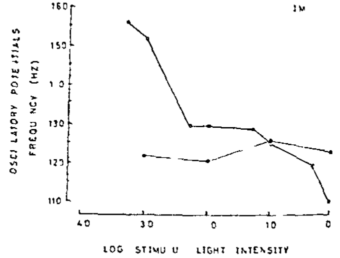


Fig 11

Dominant frequency of oscillatory potentials plotted against log stimulus light intensity of the third (stimulus) flash Black and white circles refer to the procedures described in Fig 10 When the conditioning flashes and the third (stimulus) flash were of the same intensity (white circles) the dominant frequency of oscillatory potentials decreased on succeeding stronger light adaptation and increasing stimulus intensity When the conditioning light adaptation was kept constant there was no significant change in oscillatory frequency (black circles)

3 log units No saturation of the response was noted even for the strongest stimuli used (Fig 10) The dominant frequency of the oscillatory potentials did not change significantly and was calculated to be 121–126 Hz (Fig 11) The peak latency for each individual oscillation showed a fairly uniform diminution with increasing stimulus intensity (Fig 12)

In another study the intensity of all three flashes in a series was varied and increased succeedingly from log −5 to log 0 The energy of the oscillatory potentials was low and unaltered at weak stimulation (log I = −3.3 to −2.3) There was a linear increase of the energy of oscillatory potentials with stronger stimulation (log I_s = −2.0 to 0) (Fig 10) The dominant frequency of the oscillations was around 155 Hz at threshold stimulation intensity (log I_s = −3.3) There was a subsequent decline in frequency with an increase of stimulus intensity With the strongest stimuli used the dominant frequency decreased to about 110 Hz (Fig 11) This was clearly demonstrated also on the *isolated* oscillations (Fig 8) The peak latency for each individual oscillation was also measured As to the first two oscillatory peaks the implicit time diminished about 7 msec when the stimulus intensity was increased 3 log units (Fig 13)

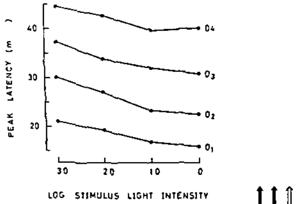


Fig 1°

Peak latencies of individual oscillatory peaks (0_1 0 0_3 0_4) as plotted against log intensity of the third (stimulus) flash from ERG s shown in Fig 9 The conditioning flashes were of constant and maximal intensity and that of the third (stimulus) flash was varied There was a fairly uniform decrease of peak latencies for all four oscilla tions The average error of repetitive calliper square readings was less than 0 5 msec Symbols of st mulation pattern as in Fig 5

However the peak latency of the third and fourth oscillatory peak showed no significant decrease

Evidently in the two experiments the same linear relation existed between the energy of the oscillatory potentials and log stimulus intensity It was found that varying light adaptation of the retina caused by conditioning flashes did not alter this linearity fundamentally although the rise of the curve occurred earlier when strong conditioning flashes were used (Fig 10)

The dominant frequency of the oscillatory potentials remained within a range of 1°0–130 Hz when the conditioning light adaptation was kept constant As the light adaptation of retina was increased the frequency of the oscillatory poten tials declined from about 155 to about 110 Hz (Fig 11)

The peak latencies for each individual oscillation showed a fairly uniform decrease and the intervals between individual peaks remained unaltered provided that the conditioning light adaptation was constant (Fig 12) With increasing light adaptation of the retina the peak latencies of the third and fourth oscillations were not significantly altered despite augmented stimulus intensity The time intervals between individual peaks were comparatively short when recorded in response to weak stimulation (around log $I_s = -3$) which by a Fourier analysis was calculated and found to be a high frequency

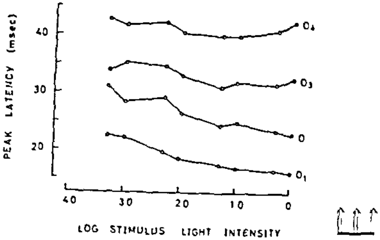


Fig 18
Peak latencies of individual oscillatory peaks (O_1 O_2 O_3 O_4) as plotted against log intensity of the third ((stimulus) flash from ERG s shown in Fig 7 The two conditioning flashes and the third (stimulus) flash had the same intensity Peak latencies for the first two oscillations (O_1 O_2) declined on increasing stimulus intensity Peak latencies for O_3 and O_4 showed no distinct change The same error of measurements as in Fig 13 Symbols of stimulation pattern as in Fig 5

(about 155 Hz) As the stimulus intensity increased from log I = − 3 3 to log I = 0 the time intervals between each individual oscillatory peak were prolonged (Fig 18) The total interval between the first (O_1) and the last oscillatory peak (O_4) expanded likewise from about 20 msec to about 26 msec and a calculation by means of a Fourier analysis displayed a dominant frequency of about 110 Hz

Discussion

The energy of the oscillatory potentials of LRG and the shape and size of each individual oscillatory peak are dependent on the intensity of light stimulus and the state of retinal adaptation The oscillations sensitively reflect an adaptation to previous short flashes of light which cause rapid or neural retinal adaptation

In dark adapted eyes the large oscillations are known to vanish (Algvere 1968 DeMolfetta Spinelli & Polenghi 1968) It is difficult to study the oscillations at threshold in complete dark adaptation since the comparatively strong

stimuli required will alter the state of retinal adaptation considerably In the present study a steady state of retinal adaptation was created by stimulation at constant intervals (every 30 sec) after a dark adaptation of 30 min This interval was found to be the most suitable for eliciting large oscillatory potentials (Fig 5) It was also observed that conditioning flashes of the highest intensity available facilitated the regeneration of large oscillations weaker conditioning flashes being insufficient (Fig 6)

The low threshold for the scotopic b wave was found at a stimulation intensity of log – 6 0 A distinct photopic b wave was seen at log I = – 4 0 A dual peaked a wave appeared at log I = – 3 3 and after conditioning flashes at log I = –3 0 Traces of oscillations were recorded at approximately the same stimulation intensity as the a wave The oscillations evoked at threshold differed however in frequency from the high intensity oscillatory response This frequency was not fundamentally changed when the state of adaptation was kept constant

In the corneal ERG the a wave does not appear until strong stimulation is used and a large b wave is then elicited The *intraretinal* a wave has in fact a lower threshold than the b wave as demonstrated in the cat eye by replacing the vitreous by a non conducting oil (Arden & Brown 1965) It is evident that thresholds *per se* of retinal electric responses are not adequately recorded by a corneal electrode This might be due to the conductive properties of the eye bulb The orientation of electric dipoles in the retina (in a tangential or radial direction) largely defines the size of the potentials recorded from cornea The a wave and b wave are oriented fundamentally in a radial direction (Brown 1968) The oscillatory potentials however have been considered to be mainly tangentially oriented (Brindley 1956) Nor do the oscillations pass through an amplitude maximum where the b wave is maximum when recorded by a micro pipette electrode during a penetration of the retina (Brown 1968)

At low stimulus intensities retinal electric responses are known to be of the scotopic type as is also seen in Fig 4 No oscillatory potentials are visible at low stimulus intensities even when recorded after conditioning flashes of light When the stimulation intensity increases a photopic b wave is evoked and cones are probably activated The oscillatory potentials are recorded by a corneal electrode at approximately the same stimulus intensity as the a wave and photopic b wave The spectral sensitivity of the photopic b wave corresponds to the perceptival photopic luminosity curve of the human eye (Johnson Riggs & Schick 1966) The maximal spectral sensitivity of the oscillations is likewise found in the red end of spectrum (Rouher Sole & Alfieri 1966) After strong and repetitive light stimulation the organization of retinal neural pathways and receptive fields are likely to change into a photopic

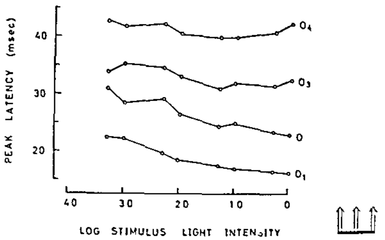


Fig 18

Peak latencies of individual oscillatory peaks (O_1 O O_3 O_4) as plotted against log intensity of the third ((stimulus) flash from ERG s shown in Fig 7 The two conditioning flashes and the third (stimulus) flash had the same intensity Peak latencies for the first two oscillations (O_1 O) declined on increasing stimulus intensity Peak latencies for O_3 and O_4 showed no distinct change The same error of measurements as in Fig 17 Symbols of stimulation pattern as in Fig 5

(about 155 Hz) As the stimulus intensity increased from log I $= -3\ 3$ to log I_s = 0 the time intervals between each individual oscillatory peak were prolonged (Fig 13) The total interval between the first (O_1) and the last oscillatory peak (O_4) expanded likewise from about 20 msec to about 26 msec and a calculation by means of a Fourier analysis displayed a dominant frequency of about 110 Hz

Discussion

The energy of the oscillatory potentials of ERG and the shape and size of each individual oscillatory peak are dependent on the intensity of light stimulus and the state of retinal adaptation The oscillations sensitively reflect an adaptation to previous short flashes of light which cause rapid or neural retinal adaptation

In dark adapted eyes the large oscillations are known to vanish (Algvere 1968 DeMolfetta Spinelli & Polenghi 1968) It is difficult to study the oscillations at threshold in complete dark adaptation since the comparatively strong

oscillatory peak latencies is a mere consequence of the shortening of latencies for the slower potentials (a and b waves)

When the retinal adaptation to light proceeded there was a significant chan e in frequency of the oscillations from 150–160 Hz to 110–120 Hz Such a change in oscillatory frequency was also observed when the intervals between flashes were shortened and retinal light adaptation increased (Algvere & West beck 197?) The dominant frequency of the oscillatory potentials varies with the retinal adaptation caused by short flashes of light This relationship illustrates the intimate connexion of the oscillatory potentials with rapid retinal processes of adaptation

This behaviour is consistent with the contrasting effects of adaptation on the amplitude and latency of the b wave as observed in the rat the implicit time bein defined by the intensity of stimulation and the amplitude by the adapta tion (Cone 1964) Generally the timing and amplitude of retinal electric responses vary independently of one another and vary even in certain diseases of the human eye (Berson Gouras & Hoff 1969)

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pattern (Barlow Fitzhugh & Kuffler 1957) Thereafter certain prerequisite conditions seem to be fulfilled enabling large oscillatory potentials to develop

The oscillations show several behavioural characteristics similar to the transient amacrine cell response recorded by intracellular microelectrodes from the Necturus retina (Werblin & Dowling 1969) This similarity is also supported by the "proximal negative response" regarded as an extracellular field potential regenerated from the amacrines of the frog retina (Burkhardt 1970) According to Dowling (1970) amacrine cells act as true interneurons between certain bipolar cells and ganglion cells It is considered that the amacrines are activated principally at onset and cessation of light stimulus and seem to accentuate changes in retinal illumination It has also been suggested that the transient type retinal responses may play a part in the directional selectivity mechanisms (Norton Spekreijse Wagner & Wolbarsht 1970) and respond to moving stimuli (Werblin 1970) Such behaviour must be regarded as a typically photopic function facilitated in the light adapted retina

After strong repetitive flashes of light the retina evidently becomes organized so that oscillations can develop Thus it seems not unreasonable to assume that the transient amacrine activity might be transmitted to the corneal ERG appearing there as oscillatory potentials

There was a linear relation between the energy of oscillatory potentials and log stimulus intensity when the conditioning flashes were identical with those of stimulation This is not unexpected since the a and b waves are known to show the same relation within a large range of intensity (Granit 1947) The effect of conditioning flashes is remarkable When these are strong enough the oscillatory response gains in amplitude This was also observed when a double flash stimulation was performed during the course of dark adaptation (Algvere & Westbeck 1972) With conditioning flashes of weak intensity the oscillations are recorded minute and indistinct

The linear relation between log stimulus intensity and oscillatory energy extends over 3 log units and presumably more since no saturation of the response occurred with the stimulus intensity used When stronger stimuli are applied there will be a decline of oscillatory energy since the ERG especially the b wave is suppressed by the light adaptation induced If the experiment is continued longer stimulation intervals are necessary and the steady state of retinal adaptation is abandoned

Provided that the state of retinal adaptation was kept constant the peak latencies of respective oscillatory peaks diminished quite uniformly on augmentation of light stimulation over 3 log units of intensity These observations are consistent with the studies of Bornschein & Goodman (1957) performed within a relative intensity range of 1 to 16 It is not known whether the decline of

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HYPOTHYROIDISM IN PROGRESSIVE OPHTHALMOPATHY OF GRAVES DISEASE

BY

SVEN ALMQVIST and PEEP ALGVERE

Thirty patients with Graves disease and progressive ophthalmopathy which required pterional orbital decompression were followed from 1964 to 1971 regarding their general health and thyroid and eye functions
Twenty patients developed progressive ophthalmopathy after radio iodine treatment 9 after subtotal thyroid resection and 1 during neomercazole treatment
Twenty five of 30 patients had documented hypothyroidism after the treatment of their basic disorder In every case the ophthalmopathy started or became progressive during the period of hypothyroidism A remarkably acute onset of ophthalmopathy was reported in nine cases within four weeks of antithyroid therapy Another nine patients developed slight hypothyroidism but displayed an ophthalmopathy one year or more after the basic treatment Five patients without documented hypothyroidism developed progressive ophthalmopathy two months to 5 years after therapy
Seven patients had recurrent Graves disease and in five of these a deterioration of ophthalmopathy occurred during the recurrent episodes
The hypothyroidism developing after treatment of the hyperthyroidism of Graves disease seems to be a major pathogenic factor in progressive ophthalmopathy

Key words progressive – infiltrative endocrine ophthalmopathy – exophthalmos hypothyroidism – *Graves* disease – surgery – orbital decompression

Abbreviations h TSH = human thyrotrophin LATS = long acting thyroid stimulator EPS exophthalmos producing substance

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VARIA

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With the help of the Prof Dr H J Fleringa Foundation the Intraocular Implant Club offers an Award of at least $ 1000 plus a medal for the best original work in the field of intraocular artificial lenses The award is open to every scientific discipline

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2nd International Symposium on Orbital Disorders

The Orbital Centre of the Wilhelmina Gasthuis Academic Hospital University of Amsterdam is organising a Symposium on Orbital Disorders in 1973 on May 28th 29th and 30th

This Symposium will cover aspects of the diagnosis treatment and pathology of primary and secondary disorders of the orbit

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The place of meeting R A I Congress Centre Amsterdam Holland

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Case Material

In 34 patients (28 females and 6 males) with severe endocrine ophthalmopathy and progressive proptosis lateral decompression of the bony orbit was performed in 60 eyes during the period 1964–1971 The operation was carried out bilaterally in 26 patients and was limited to one orbit in 8 patients In 4 patients there were not data enough to retrospectively evaluate the endocrinologic disease in detail These cases were excluded from the main case material

In the main material evaluated (30 patients) the patients ages at the time of orbital surgery varied from 31 to 71 years (average 53 years) Hyperthyroidism was present in all patients with an average duration of 3 1 years as calculated from the 95 percentile (range 1/2–11 years) One patient had had known thyrotoxicosis with ophthalmopathy for about 30 years

All patients had been under continuous medical and ophthalmologic control

Methods

A DIAGNOSTIC PROCEDURES

The notes on the 34 patients have been retrospectively scrutinized in the Departments of Endocrinology Ophthalmology Neuro surgery and Radiotherapy The course of the thyroid function and ophthalmopathy was followed clinically on many occasions during one year and also evaluated by regular measurements of the pituitary thyroid function (PBI T_3 resin and 24 hour uptake of ^{131}I)

The existence and degree of hypothyroidism were based on a synthesis of the clinical evaluation and laboratory measurements in a specialized thyroid out patient unit for hypothyroidism and progressive ophthalmopathy Symptoms and signs of hypothyroidism disappeared when thyroxine was administered in maximum tolerable doses The PBI measurements at our hospital from 1964–1971 identified only about half of all obviously hypothyroid patients and usually the PBI levels in patients with developing hypothyroidism decreased to low values (PBI 3 8 µg%) after a lag of several months to half a year Determinations of h TSH have roughly doubled the frequency of clinically verified hypothyroidism (Almqvist & Karlberg in press)

B THERAPEUTIC METHODS

The following therapeutic methods have been used according to the needs of each patient

A benign and slight ophthalmopathy often occurs in any phase of the course of hyperthyroidism (here restricted to Graves disease) This ophthalmopathy may include some proptosis of the eye bulbs and symptoms and signs secondary to the increased sympaticotonus in Graves disease and usually regresses when thyroid function returns to normal In very few of these patients does ophthal mopathy progress and become infiltrative or malignant to result untreated in irreversible sequelae

The nature of this rare ophthalmopathy is not clear but can be described grossly as a striking myopathy of extrinsic ocular muscles and infiltrative changes of most orbital structures (Naffziger 1933 Smelser 1962 Kroll & Kuwabara 1966) with functional loss of motion of the eye (infiltrative oph thalmopathy") and vision (malignant ophthalmopathy)

The etiology and pathogenesis of infiltrative and malignant ophthalmopathy in man are largely unknown as are its prevention and therapy In fact oph thalmopathy appears to be one of the greatest challenges in current thyroido logy No qualitative or quantitative clue to the underlying nature of the ocular changes has been given even by the most modern chemical tools including isolation and quantitation of intraorbital glycosaminoglycans (Prime 1968) LATS by many workers bound to one immunological mechanism for the development of Graves disease seems not to be specifically connected to ophthalmopathy (Ingbar & Woeber 1966) In Graves disease involving eye changes pituitary TSH is normal or low in serum and injection of h TSH does not cause ophthalmopathy ESP has never been quantitatively related by satisfactory methods to the course of the disease The β chain of TSH has been shown to produce proptosis in fish (Winand 1970) Thyroid hormones have not been observed to cause infiltrative ophthalmopathy in cases of iatrogenic hyperthyroidism In primary hypothyroidism infiltrative ophthalmopathy seems to be very rare Fox & Schwartz (1967) described one case and made reference to 46 cases in the literature

None of the tools available to treat hyperthyroidism e g the administration of radio iodine antithyroid drugs or subtotal thyroidectomy *per se* cause in filtrative ophthalmopathy in man

This paper presents 34 patients with Graves disease who developed progres sive ophthalmopathy and were observed for 1–7 years The hypothyroidism as a sequel of therapy for Graves disease is considered to be a crucial pathogenic factor in infiltrative ophthalmopathy This case material includes only those eyes which in spite of conventional endocrinologic and ophthalmologic treat ment progressed to a stage where surgical intervention by means of a pterional decompression of the orbit was considered necessary

Table I

Distribution of euthyroid and hypothyroid patients post therapy coinciding with progression of infiltrative or malignant ophthalmopathy

	Euthyroidism	Hypothyroidism			
Number of patients		With progressive ophthalmopathy			Without progressive ophthalmopathy
	5	25			0
		Coming after treatment of Graves disease with			
		$Na^{131}I$	Thyroid surgery	Antithyroid drugs	
		16	8	1	
Patients sex and initials					
	F R A	F GA	F AA	F EL	
	F AB	F BB	M BA		
	M OL	F SC	F SA		
	F EN	F IE	F DG		
	F SW O	F EH	F AI		
		F SH	F KS		
		M RI	F SH		
		F BL	F LP H		
		F IO			
		F AS			
		F ET			
		F IU			
		F BO			
		M KK			
		F GS			
		F SO			

ophthalmopathy within one month of therapy Only five patients (Table I) had no verified hypothyroidism but their h TSH levels had not been measured and these patients developed a progressive ophthalmopathy later i e from 9 months to 2 5 years after therapy

The nine patients who developed progressive ophthalmopathy one year or more after therapy had a less pronounced but still obvious hypothyroidism (Table II) Generally the rate of progression and degree of ophthalmopathy were directly related to the degree of hypothyroidism (Table II)

Another relationship was studied between the number of true recurrences of

Subtotal resection of thyroid gland
Administration of therapeutic fractionated doses of ^{131}I
Treatment with antithyroid drugs such as thiouracil 100 mg 4 times daily
Substitution therapy with synthetic thyroid hormones
X irradiation and ^{60}Co treatment 4 000 rad tumour dose against the pituitary gland and the retrobulbar orbital space (Dahl 1956)
Oral administration of prednisolone 40–60 mg daily
Lateral decompression of the orbit according to Welti & Offret as performed by Backlund (1968)
Topical therapy of the eye

Observations and Results

Thyroid function and progressive ophthalmopathy

Progressive ophthalmopathy occurred after any definitive treatment for hyperthyroidism. During the period 1964–1971 a total of 34 patients with progressive ophthalmopathy that required pterional orbital decompression were admitted to our hospital. In every case the basic disorder was Graves' disease. Twenty of the patients in the main material (30 cases) developed progressive ophthalmopathy following administration of therapeutic doses of radio iodine, 9 after subtotal thyroid resection and 1 while being treated with neomercazole.

Twenty five of 30 patients who underwent orbital decompression for progressive ophthalmopathy had developed demonstrable hypothyroidism as a result of treatment of their hyperthyroidism (Table I). The ophthalmopathy started or became progressive in each one of the 25 patients during a period when they were hypothyroid. None among our 30 patients with Graves' disease developed hypothyroidism without simultaneous progression of ophthalmopathy. *Five of the 30 patients had never been diagnosed* as being hypothyroid; nevertheless their ophthalmopathy progressed. Their thyroid function was followed only by PBI levels and not by serum h-TSH. Only one of the five patients had recurrent hyperthyroidism (Table III, O.I.). Four patients had their basic disorder treated by Na ^{131}I and one by surgery.

A striking and rapid acute onset of progressive ophthalmopathy – less than four weeks after therapy for Graves' disease – was observed in nine out of 30 patients (three after thyroid surgery and six after radio iodine treatment) (Table II). Three of the nine cases (A.S., I.P., H. and C.S.) developed hypothyroidism within two weeks after surgery. Three other patients (B.B., S.H. and A.I.) had the most pronounced hypothyroidism and developed progressive

Table III

Relationship between progressive ophthalmopathy and recurrent hyperthyroidism in the case material (n = 34)

Patients (n = 7)		Progressive ophthalmopathy			No of recurrences	Later hypothyroidism
Initials	Eye no	Increased	Decreased	None		
A A	5 + 6	+			2	yes
I E	15 + 16	+			4	no
B L	17	continuous			2	yes
K H	19	+			?	yes
O L	?5 + ?6			+	2	no
I O	40 + 41	+			2	yes
S O	?	+			2	yes

Case reports

The notes on some patients illustrate very well certain aspects of the course of progressive ophthalmopathy

K K male age 75 years (Fig 1) had Graves disease without eye symptoms before therapy Antithyroid drugs were given (Thacapzole 20–40 mg daily) for ? years starting 5 months after the debut of cardiac insufficiency Untreated the cholesterol was *low* (85–11? mg%) and T_3 resin index high (170 %) After 4 months on Thacapzole the patient became clinically hypothyroid and PBI was ?4 μg/100 ml Synthetic thyroxine was given in a low dose 0 10 mg daily Four months later the patient displayed bilateral proptosis limited motion of both eyes with diplopia and decreased visual acuity of the right eye Thyroxine was discontinued and 3 months later i e after 1? months of antithyroid drugs the patient became still worse and hypothyroid (PBI was 1? μg) Hertel values ?6/?? mm visual acuity right 0? left 1 0 Synthetic thyroxine was adequately supplied (0 ?0 mg × 1) with some regression of the proptosis 24 ? mm improvement of vision 0 7 (right) 1 0 (left) and increased motion of both eyes within 1 month After 13 months the patient was euthyroid with normal PBI ?? g/100 ml and h TSH ?6 units/ml (normal values 11–?5 units/ml) Oral thyroxine was reduced from 0 ?0 to 0 15 mg daily which induced a second period of progression of his ophthalmopathy within weeks after a reduction of the dose of thyroxine This time vision decreased to 0 ? on both eyes Oral thyroxine was increased again to 0 ?0 mg daily At 16 months the patient underwent pterional decompression on both orbits His proptosis disappeared and vision increased to 0 8 (right) and 1 0 (left) After 18 months his oral thyroxine was decreased from 0 ?0 to 0 05 mg daily Two weeks later he entered his third period of progression of ophthalmopathy his visual acuity was decreased to 0 (right) and 0 1 (left) and he was hypothyroid on Thacapzole 10 mg 3 times daily This deterioration of his ophthalmopathy was not relieved on adequate substitution therapy with thyroxine

Table II
Maximal time after therapy for the development of progressive ophthalmopathy and degree of coinciding hypothyroidism

Case		Therapy	Progression of ophthalmopathy		Simultaneous degree of hypothyroidism (0 → +++)
Initials	Eye no		Years	Months	
R A	1 + 2	^{131}I		2	0
A A	3 + 4	surgery		fast	?
G A	5 + 6	^{131}I	4		++
B A	7 + 8	surgery		1	+
S A	9	surgery		4	?
B B	10 + 11	^{131}I		1	+++
A B	12 + 13	^{131}I	2½		0
S C	14	^{131}I	< 1	?	++
I E	15 + 16	^{131}I	1		0
D G	17 + 18	surgery	11		++
K H	19	^{131}I		8	+
S H	20 + 21	^{131}I		1	+++
A I	22 + 23	surgery		1	+++
R I	24	^{131}I		1	+
O I	25 + 26	^{131}I		6	++
B I	27 + 28	^{131}I		1	++
E N	29	^{131}I	progression	before therapy	0
I O	30 + 31	^{131}I		3	++
K S	32 + 33	surgery		4	++
A S	34 + 35	^{131}I		½	+
E T	36 + 37	^{131}I	1½		++
S W O O	38 + 39	surgery		10	0
I Ö	40 + 41	^{131}I		3	++
E I	42 + 43	antithyroid		3	++
B O	44	^{131}I	1		?
S H	45 + 46	surgery	1		++
K K	47 + 48	^{131}I		9	++
L P H	50	surgery		½	+
G S	51	^{131}I		½	+
S O	52	^{131}I		< 6	++

hyperthyroidism and progression of ophthalmopathy (Table III) Five out of seven cases with recurrent hyperfunction of the thyroid gland showed clear progression of their ophthalmopathy during the recurrence of their basic thyroid disorder Four of these five patients later developed hypothyroidism

Table III

Relationship between progressive ophthalmopathy and recurrent hyperthyroidism in the case material (n = 34)

Patients (n = 7)		Progressive ophthalmopathy			No of recurrences	Later hypothyroidism
Initials	Eye no	Increased	Decreased	None		
AA	5 + 6	+			9	yes
IE	15 + 16	+			4	no
BL	17	continuous			2	yes
KH	19	+			2	yes
OL	25 + 6			+	2	no
IU	40 + 41	+			2	yes
SO	5?	+			9	yes

Case reports

The notes on some patients illustrate very well certain aspects of the course of progressive ophthalmopathy

KK male age 75 years (Fig 1) had Graves disease without eye symptoms before therapy Antithyroid drugs were given (Thacapzole 90–40 mg daily) for 2 years starting 5 months after the debut of cardiac insufficiency Untreated the cholesterol was low (35–119 mg%) and T_3 resin index high (170%) After 4 months on Thacapzole the patient became clinically hypothyroid and PBI was 9 4 µg/100 ml Synthetic thyroxine was given in a low dose 0 10 mg daily Four months later the patient displayed bilateral proptosis limited mot on of both eyes with diplopia and decreased visual acuity of the right eye Thyroxine was discontinued and 3 months later i e after 1? months of antithyroid drugs the patient became still worse and hypothyroid (PBI was 1 g) Hertel values 96/95 mm visual acuity right 0 9 left 1 0 Synthetic thyroxine was adequately suppl ed (0 0 mg × 1) with some regression of the proptosis 24 mm improvement of vision 0 7 (right) 1 0 (left) and increased motion of both eyes within 1 month After 13 months the patient was euthyroid with normal PBI 5 8 g 100 ml and h TSH 96 units/ml (normal values 11– units/ml) Oral thyroxine was reduced from 0 0 to 0 15 mg daily which induced a second period of progression of his ophthalmopathy within ? weeks after a reduction of the dose of thyroxine This time vision decreased to 0 9 on both eyes Oral thyroxine was increased again to 0 90 mg daily At 16 months the patient underwent pterional decompression on both orbits His proptosis disappeared and vision increased to 0 8 (right) and 1 0 (left) After 18 months his oral thyroxine was decreased from 0 90 to 0 05 mg daily Two weeks later he entered his third period of progression of ophthalmopathy his visual acuity was decreased to 0 2 (right) and 0 1 (left) and he was hypothyroid on Thacapzole 10 mg 3 times daily This deterioration of his ophthalmopathy was not relieved on adequate substitution therapy with thyroxine

Patient A I aged 47 years had a mild uncomplicated hyperthyroidism without eye symptoms Bilateral infiltrative and malignant ophthalmopathy started very acutely within a few days after subtotal thyroid resection

Patient B B had at the age of 49 years a hyperthyroidism and benign proptosis for 6 months She was given radio iodine treatment and developed within 1 to 3 months a clinically severe hypothyroidism with low PBI (2 2 $\mu g\%$) There was an acute progression of proptosis to 27 mm (right eye) and 28 mm (left eye) decrease of visual acuity to 0 3 (right eye) and 0 6 (left eye) and intensive photophobia

The notes on patient I O aged 33 years show that after treatment for her hyperthyroidism she developed a clinical hypothyroidism despite having a PBI level within the normal range Treatment with thyroxine removed her signs of hypofunction

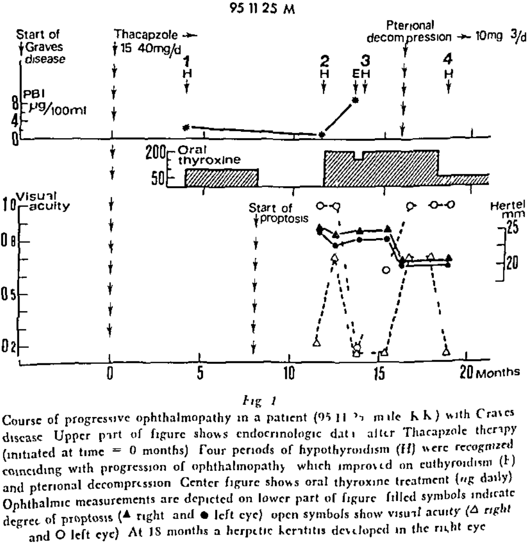


Fig 1

Course of progressive ophthalmopathy in a patient (95 11 25 male K K) with Graves disease Upper part of figure shows endocrinologic data after Thacapzole therapy (initiated at time = 0 months) Four periods of hypothyroidism (*H*) were recognized coinciding with progression of ophthalmopathy which improved on euthyroidism (E) and pterional decompression Center figure shows oral thyroxine treatment (μg daily) Ophthalmic measurements are depicted on lower part of figure filled symbols indicate degree of proptosis (▲ right and ● left eye) open symbols show visual acuity (*△ right* and O left eye) At 18 months a herpetic keratitis developed in the right eye

Discussion

This study presents some new observations on the pathogenesis of progressive ophthalmopathy Hypothyroidism induced by treatment for Graves disease is shown to be related to the development of progressive ophthalmopathy Evidence for this is based on (i) the fact that almost all (25/30) patients had hypothyroidism (ii) the correlation in time between the development of hypo thyroidism and progressive ophthalmopathy and (iii) the similarity in severity of these two phases of Graves disease

Our methods for diagnosis and measurement of thyroid function were the best available – although admittedly crude Radio immunoassay of serum TSH is now established as the safest tool for diagnosing hypothyroidism in its early stage and for following the course of the disease in adults If this method had been used in all cases a higher incidence of hypothyrodism probably would have been demonstrated since the increase in positive results was great when TSH assays were used compared to PBI measurements in early hypothyroidism (Almqvist & Karlberg in press) On the other hand several patients developed progressive ophthalmopathy before they were treated for hyperthyroidism These cases show that thyroid hypofunction after treatment is neither the first nor the only pathogenic factor in progressive ophthalmopathy

Hypothyroidism causes an increase in volume of several tissues in the body and also seems to involve the orbital space This may produce circulatory con gestion in the orbit and create an irreversible progression of the ophthalmo pathy At this relatively late stage only orbital decompression may be helpful while thyroxine substitution for hypothyroidism would not relieve the increased intraorbital pressure as it may do before local intraorbital stasis occurs

It appears that patients who developed hypothyroidism after treatment also showed a debut or progression of ophthalmopathy This fact together with recent knowledge of the high incidence of hypothyroidism after surgery or radio iodine therapy or during antithyroid drug treatment of Graves disease indicates that these measures are only part of the treatment for hyperthy roidism Each patient requires continued observation during the rest of the course of their basic disorder It is suggested that future treatment of Graves disease should include the use of methods sensitive enough to prevent the patient from suffering untreated even short periods of iatrogenic hypo thyroidism

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CORNEAL CHANGES FOLLOWING OPERATION FOR STRABISMUS (RECTUS SURGERY)

With Special Reference to Occurrence of Dellen

BY

LISBETH REEH PEDERSEN

The corneal changes directly follow ng strabismus surgery have been studied in a series of 44 patients subjected within a period of six months to th s operation in the Eye Department Kommunehospitalet Copenhagen The investigation concentrated particularly on the occurrence of Dellen Corneal anomalies were noticed in just over half of these patients Fifteen f these presented transitory changes consisting in localized stainabil ty and in some cases also transitory defects of the precorneal film were noted Dellen were found in four patients and kerat tis like corneal infiltrations n five

None of the patients devel ped permanent sequelae

Of a control group comprising 1 summoned patients previously subjected to squint operation n ne had corneal changes

The pathogenesis of Dellen is discussed We are inclined to support Bar aquer s theory that the corneal film has a share in the Dellen formation due to local breaks of th s film such having been seen prior to development of Dellen.

K y word Dellen – precorneal film – infiltrations – vital staining – strabismus ope at on

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The corneal changes called "Dellen" were first described by F Fuchs in 1911 They occur as ellipsoid excavations in the cornea close to the limbus most often temporally They are about 1½ by 2 mm in size with their longest axis parallel with the limbus They are sharply delimited with a steep wall towards the cornea and a flatter slanting border towards the limbus

A Fuchs (1929) has since pointed out as the most characteristic feature of Dellen their frequent manifestation as dark shadows on the anterior iris surface in focal light on the iris Allegedly this phenomenon is particularly frequent in cases of light irides

According to E Fuchs these corneal changes are transient (lasting about 48 hours) As *causes* he mentions 1) perilimbal elevations due to episcleritis angioma pinguecula subconjunctival injections and rectus surgery among others 2) *cocaine administration* 3) *cataract extraction* 4) *hemeralopia* 5) paralytic exophthalmos and 6) inexplicable spontaneous occurrence in elderly individuals In this connection it is interesting to note that Gaule as early as 1891 observed *small* spots or opacities in the corneal surface after *trigeminus* denervation

In addition to A Fuchs the following writers have since given accounts of Dellen in the literature Hartmann (1957) Hudelo (1957) Vancea et al (1960) Barraquer (1965) and Baum et al (1968) Norn (1969) found no Dellen among 138 patients examined for corneal lesions Hartmann Hudelo Vancea et al and Nauheim found Dellen to be most frequent among patients recently operated for strabismus The corneal changes in these cases were situated within the limbus and off the horizontal muscle into which the cut had been made Barraquer described occurrence of Dellen not only after rectus surgery but also in relation to many of the pathological states mentioned by F Fuchs e g in an antiglaucomatous filtration swelling following operation for glaucoma and in pterygium Baum et al like Barraquer mention different causes of Dellen such as cataract extraction rectus surgery subconj haemorrhages and conjunctival carcinoma

Some disagreement seems to prevail regarding the *duration* of Dellen As stated above E Fuchs described Dellen as transient phenomena lasting at most *48 hours* The majority however take the phenomenon to be more prolonged lasting a few days to several weeks Baum et al have mentioned Dellen lasting for about one year but this is probably an exception Dellen most often occur within one or two weeks of operation for strabismus (Vancea et al Baum et al)

The *patho-anatomical* changes in Dellen were first described by F Fuchs (1911) who noticed a thinning down of the corneal epithelium the underlying stroma and Bowman s membrane A Fuchs (1929) has probably given the most

detailed description of the changes He undertook histological examination in a single case and found thinning down of the epithelium the upper stromal layer and Bowman s membrane at the site of Dellen In addition he observed a regular epithelial defect centrally in the excavation with absent or an extremely thin epithelial covering A Fuchs found epithelial proliferation along the border of the excavation The epithelial defect centrally in the Dellen must therefore be expected to be vital stained by fluorescein as also described later by Vancea et al (1960)

Material

The present investigation of the postoperative corneal changes after operation for strabismus was based on a series of 44 patients operated on in the Eye Department Kommunehospitalet Copenhagen within a six month period from Dec 15 1968 to June 15 1969 Not all patients subjected to squint operation within this period could be included in the investigation A few young infants unable to co operate had to be ruled out

Further a control group of 21 patients previously operated on for strabismus were summoned for a follow up These were patients operated on in the stated unit about 1–2 years before the present investigation was undertaken

Age incidence in the group of recently operated patients

The patients ranged in age from 2 to 32 years with children predominating The age incidence was as follows

0– 5 years 18 patients (8 males and 10 females)
5–10 years 10 patients (6 males and 4 females)
10–15 years 12 patients (3 males and 9 females)
15–20 years 3 patients (1 male and 2 females)
> 20 years 1 patient (female)

Sex incidence 18 males 26 females

Surgical technique and postoperative measures In 43 of the 44 patients the surgical intervention concentrated on the rectus muscles while one patient had the obliquus inf retroposed The great majority of the 43 rectus operations consisted in advancement and recession of recti of the same eye (38 patients) while in two patients the operation was limited to one rectus (recession of the medial) In the remaining three patients bilateral recession of the medial rectus was performed Fixation sutures were employed during the operation in all cases except one

Suture material used 5–0 catgut for recession 4–0 for resection The conjunctiva was sutured either with continuous catgut or by knotted cutgut sutures (5–0)

Postoperatively all the patients had chloramphenicol ointment applied to the operated eye No dressing

Procedure

The first two or three days after the operation all the patients were examined once daily in the slit lamp In the majority of cases this examination was performed while the patient was still in hospital the usual 24–hour postoperative stay having as far as possible been prolonged by one or two days Within the first week after their discharge all the patients were examined once or twice in the out patient eye department In the cases with corneal changes the control was continued as long as fresh changes were noticed One patient s control period extended over five months

The eyes were subjected to *slit lamp examination* allowing assessment of the following factors

1) The degree of perilimbal conjunctival swelling at the site of operation

2) *Appearance of the precorneal film* The film was rendered visible by instillation of 1 % fluorescein and immediately examined in a Haag Streit slit lamp No 900 in the blue cobalt filtered light entering obliquely as a 1–2 mm broad vertical pencil of rays (cf Norn 1969) While the pencil of rays was moved slowly from side to side across the cornea the examiner could notice defects in the fluorescein stained film which if present manifested themselves as dark areas

3) *Vital stained regions* stained partly by fluorescein and partly by rose bengal The fluorescein stainability known to be a sign of epithelial defects was studied in connection with the evaluation of the precorneal film likewise in the blue cobalt filtered light

Rose bengal stainability was studied in the white slit lamp light after instillation of 0 01 ml of a 1 % solution (from a needle mounted tube)

4) *Corneal excavations* (Dellen) or possible other pathological changes were investigated by means of a narrow pencil of rays entering obliquely and thus disclosing irregularities if present of the corneal surface The thickness of the cornea could also be estimated

Results

The phenomena recorded have been set out in Table I

Table I

Conjunctival swelling	in 44 pts (all)
Defects in the precorneal film	in 12 pts
Fluorescein stainability	in 19 pts
Rose bengal stainability	in 21 pts
Infiltrations	in 5 pts
Dellen	in 4 pts

Re 1) More or less pronounced swelling off the site of operation was noticed in all 44 patients The conjunctival reaction seemed to be most pronounced in the patients presenting postoperative corneal changes The conjunctival swelling subsided in most cases within one or two weeks after the operation In some instances it persisted for a longer time and a small number of patients had to be given local treatment with chloramphenicol or neocortol to reduce the reaction

Re 2) Corneal changes In 20 of the 44 patients i e in a scant half no corneal changes whatever were observed

Among the remaining 24 patients pathological conditions differing in intensity were found Thus 15 presented changes which must be characterized as modest while nine displayed more pronounced abnormalities

The pathological changes were grouped as follows

Epithelial changes In ten patients the changes noticed in the corneal surface were in all probability due to contact of the fixation suture with the corneal surface during the operation These changes were of only a few days duration and consisted in local stainability with rose bengal or fluorescein In rare cases transitory defects of the precorneal film were seen as well The most frequent finding was that of a broken line fluorescein staining running a horizontal linear course corresponding to the site of the suture

Five patients presented similar changes except that the linear epithelial defects in these cases ran a vertical course within the limbus off the sites of operation in a direction opposite to that of the supposed position of the fixation suture

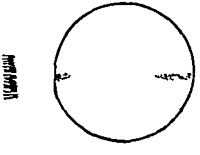


Fig 1

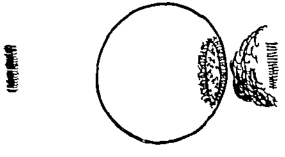


Fig 2

Corneal changes following operation for strabismus (rectus surgery)

The only patient on whom the operation was performed without fixation suture presented similar changes with vertical linear stainability This observation bears out the view that such changes are independent of the fixation suture The precorneal film was normal in this case

A common feature of these – fairly mild – corneal changes was that they all came and went within 8–14 days of the operation

The remaining nine patients displayed more prominent pathological changes These have been set out in Table II

Epithelial and stromal changes In *five* patients *infiltrations* were seen in the cornea in four of these as ca 2 × 2 mm large keratitis like infiltrations of the corneal tissue The fifth patient presented a larger and more persistent infiltration The former minor infiltrations lasted for from two or three days to maximally three weeks The affection included in all five cases both surface epithelium (vital stained) and stroma with opacity of the latter In three eyes the precorneal film was defective at the site of infiltration

In the four mild cases no sequelae developed in the form of corneal opacity after the infiltrations In the fifth case a greyish opacity of the corneal tissue persisted for several months

Postoperative *Dellen* occurred in *four* patients In three of these the excavations were noticed within 8–14 days after the operation whereas in the fourth not till about three weeks after

The excavations were all situated paralimbally just within the limbus either temporally or nasally on the cornea Dellen were most often seen located off the muscles subjected to resection (or advancement) The same was true in the patients developing infiltrations

Thus both infiltrations and Dellen were observed twice as often off the sites of resection as off the recessed muscles (cf Table II)

Table II

Cl n l fi l g n th ne p t nt w il Inf lt ti o D ll

N of patient	Age	Sex	Su g l inter vention	C nj reac tion	Day lesion n ted postop	Type of lesion	Vital staining	S te	Therapy	Du ati p t p tively a) improve ment noted	Du ati p t p tively l) t tal cure	l orn al film lefect
1	4	♀	rec l m r res l l r	+	/th day	infiltr	+ R-B + flu	3 o clock	no	14th day	21st day	+
›	11	♀	rec r m r res r l r	+ (+)	5th day	infiltr	+ flu + R-B	9 o clock	no	??nd day	29th day	—
3	4	♂	rec r m r	+ (+)	?nd day	infiltr	+ flu + R-B	3 o clock	no	ɔth day	9th day	+
4	ɔ	♂	rec r m r res r l r	+	?nd day	infiltr	+ flu — R-B	7–9 o clock	no	?	14th day	—
5	17	♀	rec l m r res l l r	+ + +	13th day	infiltr	+ flu + R-B	2–5 o clock	neocortol chl amph	19–20? day	150th day (5 mths)	+
6	?	♂	rec r m r res r l r	+ (+)	15th day	Dellen + infiltr	+ flu + R-B	(3)–4 o clock	no	?8th day	(?nd day	+
7	3	♂	rec l m r res l l r	+	1st day	Dellen	+ flu + R-B	3 o clock	no	7th day	??nd day	+
8	1?	♂	rec r m r res r l r	+	9th day	Dellen	+ flu + l -B	3 o clock	no	40th day	?8th day	+
9	11	♀	rec l l r	+ +	?3rd day	Dellen	+ flu + R-B	3 o clock 9 o clock	chl amph	40th day	?	+

rec = recessi n l = lateral m = medial r = rectus
res = resection or anteposition
a l conj reaction + = mild reaction ++ = moderate to pronounced +++ = excessive

A ph l s

A typical finding in all four patients with Dellen was that of a defective or absent precorneal film over the corneal area at which the excavation later occurred In three of the patients the defective precorneal film with local desiccation was the first disorder observed and preceded the other changes

Vital staining was noticed in all four patients with Dellen Fluorescein staining was seen in the excavation this being filled with fluorescein stained tear fluid

In rare cases slight punctate fluorescein staining was seen in the tissue indicating that presence of even minute defects in the epithelium of Dellen is exceptional

Rose bengal staining was not concentrated solely in the Dellen but was also found within a minor area of the cornea around the excavation thus disclosing groups of degenerate epithelial cells in and close to the Dellen

The *size* of the Dellen was approximately that stated by E Fuchs i e about 1½ by 2 mm Their sites and positions were likewise as he described upright within the limbus with their longest diameter vertical The steep wall towards the cornea stated by E Fuchs to be typical was seen in none of the cases under review The excavations found in these had slanting borders all around

The *duration* was somewhat longer than the maximal 48 hours stated by Fuchs ranging from two or three weeks to maximally four weeks Local treatment was given in one case only in the form of chloramphenicol drops which seemed to have no influence on the course Steroid was administered in none of the cases

Symptoms The subjective troubles of patients with corneal infiltrations differed little from those generally complained of by patients with active corneal lesions such as keratitis and erosion viz pain photophobia and streaming lacrymation

The four patients with Dellen had remarkably few symptoms and these were not more pronounced than those of the patients with no or only mild corneal changes

The *control group* comprised 21 patients operated on for strabismus in the Eye Department one or two years before the present investigation

The patients had been summoned for a follow up which was parallel in principle to the examinations to which the recently operated patients were subjected consisting of a slit lamp evaluation of precorneal film corneal surface corneal thickness stromal opacity if present and vital staining

The 21 controls all showed normal conditions None displayed any signs of a previously receded corneal lesion more particularly there was no corneal opacity

Discussion

The changes described above may give us an impression of the clinical features in the development of corneal Dellen Initially local dry areas are seen in the precorneal film These changes probably constitute the precursor of the Dellen formation They may be limited to dry spots possibly vital stained or develop further into infiltrations or Dellen with associated reduction of the corneal thickness over a local paralimbal region

Different theories have been advanced in the course of time concerning the aetiology of Dellen Most early writers inclined towards either a so called vascular theory or a neurotrophic According to the former theory the corneal thinning is due to an obstructed vascular supply and according to the latter it is attributable to a purely mechanical nerve lesion in consequence of pressure or possibly cutting during the operation

More modern writers e g Barraquer Baum A Fuchs Hartmann and Vancea et al have called attention to the importance of the precorneal film in the development of Dellen Wolff (1954) believed the precorneal film to consist of a superficial oily layer an intermediate fluid layer and a deeper mucous layer Later N Ehlers showed that the precorneal film may be regarded as a film consisting of an intermediate fluid layer covered on both sides by a lipid layer

Mishima & Maurice (1961) showed that superficial blocking of the meibomian glands of rabbits caused the outermost oily layer of the cornea to disappear They also estimated quantitatively the evaporation from the surface of the normal tear film and proved that this evaporation leads to hypertonicity of the tear fluid resulting in an increased osmotic tear flow across the cornea

Brown & Mishima found that evaporation from the corneal surface reduced the thickness of the cornea Further as also stated by other writers *e g* Hæm (19 0) and Norn (1969) they showed that slowed down or totally arrested blinking may give rise to small discrete desiccations of the precorneal film which may proceed to local excavations in the cornea Norn found eliminated wetting time in relation to different active corneal lesions e g erosions keratitis and foreign bodies Permanent holes in the protective precorneal film are thus supposed to be responsible for occurrence of paralimbal Dellen in cases of prolonged perilimbal elevations owing to the locally uneven surface level This has in fact been described in relation to subconjunctival haemorrhages subconjunctival oedema subconjunctival injections pterygium etc.

A dynamic relation to the tear fluid underlies in other words *this third and since recently more prevailing theory* concerning the share of the precorneal film in the development of Dellen *The results of the present investigation also*

seem to bear out this theory discontinuity of the precorneal film having been found before Dellen occurred as could be assessed in the slit lamp by studying the fluorescein pattern

The finding of Dellen at sites of advancement of the muscle is readily explainable by the fact that in such cases the conjunctival swelling is situated closer to the limbus than in cases with recession of the muscle

The possibility can hardly be excluded that the present investigation of the 44 patients failed to disclose Dellen of very short existence Despite the frequent observations aimed at it was impossible to carry through daily control examinations of the patients over a fairly long period particularly after they had left the unit

The spontaneous course of Dellen must thus with the above theory in mind depend on the rate at which the provoking perilimbal elevation disappears If it persists for a long time the local discontinuity of the precorneal film will continue to exist and provoke Dellen Baum concludes in his paper (1968) that promt local treatment counteracting dehydration of the cornea must be instituted to avoid cicatrisation However in none of the above cases were Dellen found to have led to grave sequelae or complications in the form of regular descemetocele formation Further the corneal thinning decreased in all cases without permanent sequelae gradually as the conjunctival swelling subsided If as advocated by Baum local therapy is to be given this must aim at reducing the perilimbal swelling as can be done by local application of steroid for instance – or consist in introduction of artificial tear fluid e g methyl cellulose or ointment Such treatment might perhaps have prevented development of Dellen in the cases under review Another possibility is that early treatment with neocortol for instance might have prevented Dellen formation The conclusion to be drawn from this is that after each operation for strabismus where the conjunctival reaction is slightly more pronounced than usual local treatment with steroid should be routine However despite the chances for the patient developing pathological corneal changes such treatment is not considered to be absolutely necessary owing to the benign clinical course of these changes with only relatively mild symptoms and gradual regression of the signs without sequelae We may probably with greater reason be justified in concluding that such treatment is to be restricted to patients showing protracted conjunctival reaction and having such pronounced symptoms that these alone indicate treatment

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CHORIOIDEREMIE UND FAMILIENBERATUNG

VON

K E KRÜGER W MOELLER und K ZERNAHLE

Ausgehend von einer Chorioideremiesippe von 21 Personen aus 3 Generationen mit 6 Erkrankten (1 Erwachsener im End und 5 Knaben im Anfangsstadium) wird zur genetischen Familienberatung bei dieser Erkrankung Stellung genommen und darüber hinaus werden Hinweise zur Verbesserung der genetischen Beratung bei Erbkrankheiten gegeben

Key words chorioid – chorioderemia – heredity

1 *Krankheitsbild* Mauthner beschrieb 1872 ein Krankheitsbild das er Chorioideremie (Ch) nannte weil es seiner Meinung nach durch ein angeborenes Fehlen der Aderhaut verursacht wurde Aus einer Vielzahl späterer Veröffentlichungen (ausführliche Literaturzusammenstellung bei Kurstjens und Waardenburg Franceschetti und Klein) wurde der progressive und hereditäre Charakter dieser Erkrankung deutlich Aber erst 1942 konnten Waardenburg und Goedbloed unabhängig voneinander den X chromosomal gebundenen intermediären Erbgang dieser Krankheit beweisen der dann 5 Jahre später von McCulloch und Mitarb an einem grossen Material mit einer Vielzahl von Stammbaumen bestätigt wurde Bis heute ist aber ungeklärt ob es einen ange

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borenen Aderhautmangel gibt und es ist auch nicht entschieden ob dieser Erkrankung primär eine Störung im Pigmentepithel (wie von Waardenburg angenommen) oder in der Chorioidea (wie von François vermutet) zugrunde liegt. Waardenburg hat für das Leiden den treffenden Terminus »progressive tapetochorioidale Degeneration« vorgeschlagen

Die Erkrankung führt meist im 5 und 6 Dezennium zur Erblindung Jede Therapie ist machtlos (Campbell Gebertt, u a) Möglicherweise gibt es auch relativ gutartige Formen bei denen die Erblindung erst später eintritt Da die hemizygoten Männer infolge ihrer Geschlechtschromosomenkonstitution nur ein Allel nämlich das defekte von ihrer Mutter erhalten haben erkranken sie im vollen Umfang Die Frauen können homozygot oder heterozygot sein wobei Homozygotie einem hemizygoten Vater und eine zumindest heterozygote Mutter voraussetzt In diesem extrem seltenen Falle würden sie wie die Männer unter dem Vollbild mit funktionellen Ausfällen erkranken Die heterozygoten Frauen sind zwar ophthalmoskopisch an charakteristischen Fundus pigmentierungen zu erkennen fühlen sich aber da sie keine funktionellen Ausfälle haben, subjektiv gesund Sie übertragen dieses Erbleiden ohne davon zu wissen. Die betroffenen Männer kommen meist erst im Endstadium der Erkrankung in die augenärztliche Sprechstunde und bieten dann das charakteristische Bild durch Schwund von Aderhaut und Netzhaut schimmert die Sklera durch und es findet sich ophthalmoskopisch ein typisch gelblich weisser Fundus in dem lediglich das Makulagebiet als inselförmiger rötlicher Bezirk ausgespart ist Am gesamten Fundus werden unregelmässige Pigmentanhäufungen angetroffen die keine Knochenkörperchen ähnlichen Strukturen zeigen Die Netzhautgefässe werden meist als normal oder nicht wesentlich verändert beschrieben (Kurstjens von Burstin u a) Diesem morphologischen Bild entspricht der funktionelle Befund röhrenförmige Gesichtsfeldeinengung bis auf winzigen zentralen Rest der dann auch verfällt Auslöschung des ERG Dunkeladaptionkurve nicht aufnehmbar Der zentrale Visus kann bis zum endgültigen Zusammenbruch noch lange relativ gut sein

Im Gegensatz zum Endstadium das unverkennbar ist bereiten die Anfangsstadien differentialdiagnostische Schwierigkeiten Im Initialstadium werden nach Kurstjens feinkörnige Pigmentierungen in der Äquatorgegend und peripher in den tiefen Netzhautschichten und auf der Höhe des Pigmentepithels angetroffen In diesem Stadium soll eine Atrophie der Chorioidea nocht nicht feststellbar sein Erst in späteren Stadien kommt es dann zur Atrophie der Chorioideagefässe und der Aderhaut von der Peripherie zum Zentrum fortschreitend Natürlich ist der Krankheitsverlauf fliessend so dass die beschriebenen Bilder der einzelnen Beobachter voneinander abweichen können In den Anfangsstadien fällt differentialdiagnostisch eine Abgrenzung zur Atrophia gyrata chorioideae et retinae (autosomal rezesssiver Erbgang) und der progressiven Chorioidea Sklerose oft sehr schwer Das morphologische Bild der Überträgerin ist durch die wechselseitige Beziehung des defekten Allels zum normalen sehr variabel und schwankt zwischen leichten Pigmentstörungen und Bildern die für Chorioideremie typisch sind (Kurstjens Krill u a)

Als wichtige Beiträge zu diesem seltenen Krankheitsbild seien die Monographien und Arbeiten von Sorsby Franceschetti Joseph und Davey Pameyer Waardenburg und Henkes Waardenburg Franceschetti und Klein, Franceschetti François und Babel Kurstjens genannt

2 *Eigener Stammbaum* Die Durchsicht der grossen Zahl von Stammbaumen in der Literatur offenbart die ganze tragische Bedeutung der Krankheit fur die Betroffenen und die anderen Familienmitglieder Mit der Problematik wie man diesen unglücklichen Familien helfen kann wurden wir durch einen 54 jahrigen Mann mit dem Endstadium der Erkrankung konfrontiert Ein Bruder des Patienten war im Laufe der letzten 15 Jahre gleichfalls erblindet Da zu befurchten war dass auch noch Familienmitglieder insbesondere die Enkelkinder erkranken können kam er in die Sprechstunde

Fur die Familienberatung haben wir alle erreichbaren Mitglieder klinisch zytogenetisch und fluorescenzangiografisch untersucht insgesamt 17 von 21 Personen aus 3 Generationen Bei 5 Knaben zwischen 5–10 Jahren fanden wir das Anfangsstadium und bei dem oben erwähnten Manne das Endstadium der Erkrankung

Über die fluorescenzangiografischen Ergebnisse werden wir gesondert berichten

Mit dem in Abb 1 wiedergegebenen Stammbaum kann auch von unserer Seite der X chromosomal gebundene intermediäre Erbgang dieser Erkrankung bestätig werden Es ergibt sich folgende Interpretation

1 Der eingangs erwähnte Patient und sein ebenfalls erkrankter Bruder besitzen das defekte X sind also hemizygot Ein weiterer Bruder und eine Schwester sind gesund

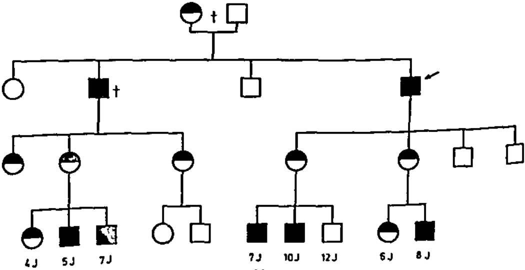


Abb 1
Stammbaum der untersuchten Sippe □ ○ normal ○ nicht undersucht ◒ heterozygote Frau ■ hemizygoter Mann



Abb 2

Chorioideremie im Endstadium Lo A 54 J mannlich Visus re Lux proj falsa li Lux proj recta. Zentraler Gesichtsfeldrest unter 5 links gelblich weisses Fundus kolorit durch Schwund von Aderhaut und Netzhaut Aussparung der Makula als rotlicher inselformiger Bezirk unregelmassige Pigmentanhaufungen Netzhautgefasse etwas eng Normaler Papillenbefund

2 Die Mutter dieser Patienten muss als heterozygote Tragerin angesehen werden

3 Die beiden mannlichen Nachkommen in der 2 Generation sind gesund alle 5 weiblichen sind Übertragerinnen

4 *Aus der Ehe dieser Heterozygoten mit gesunden Mannern konnen theo* retisch 50 % Gesunde und 50 % belastete Kinder hervorgehen darunter hetero zygote Madchen und hemizygote Jungen im Verhaltnis 1 1 In unserer Sippe ist die Belastung ausserordentlich hoch von 8 untersuchten Kindern sind 7 defekt

Klinische Befunde

Der Patient hatte bis zum 51 Lebensjahr mit einer Schminderung rechts auf Lichtwahrnehmung mit falscher Projektion und links auf 5/10 mit Korrektur bei zentralen Gesichtfeldresten von rechts unter 5 und links unter 10° noch in der Landwirtschaft als Geschirrfuhrer gearbeitet (Abb 2)[1]

Bei den 3 Knaben im Alter von 5–10 Jahren konnten wir das *Anfangsstadium* der Erkrankung studieren Das ophthalmoskopische Bild war ziemlich einfor mig Am gesamten Fundus waren in den tiefen Netzhautschichten tupflige

Pigmentierungen und Depigmentierungen zu sehen. In der Tiefe waren vereinzelte Aderhautgefässe zu erkennen, die Netzhautgefässe waren normal. Bei allen untersuchten Jungen waren die Sero-Reaktion auf Lues, Toxoplasmose, Listeriose und Bruzellose negativ.

Funktionell fanden sich im einzelnen:

1. Ra. St. Nr. 9925/71, 5 Jahre alt, Visus rechts −7,5 s = 5/35 1/8 (Pflüger-Haken), links 5/7 (Pflüger-Haken). Gesichtsfeldbestimmung und Anomaloskop-Untersuchung: keine verwertbaren Angaben.

2. Ra. Th. Nr. 9927/71, 7 Jahre alt, Visus rechts/links 5/4. Ergebnisse der Gesichtsfeldbestimmung, Anomaloskop-Untersuchung und Dunkeladaptation regelrecht.

3. Ro. B. Nr. 7592/71, 6 Jahre alt, Visus rechts −1,25 s + 0,5 cyl A 90 = 5/4, links −1,25 s + 0,5 cyl A 90° = 5/4. Gesichtsfeldaussengrenzen am Maggiore-Perimeter mit der 1 mm Marke auch nach mehrfachen Kontrollen 15–20 Grad konzentrisch eingeschränkt. Ergebnisse der Dunkeladaptation und Anomaloskop-Untersuchung regelrecht.

4. Be. H. Nr. 7595/71, 8 Jahre alt (Abb. 3), Visus rechts/links 5/4. Gesichtsfeldaussengrenzen am Maggiore-Perimeter beiderseits mit 1 mm Marke bei mehrfachen Kontrollen 20 Grad konzentrisch eingeschränkt. Dunkeladaptationskurve, Anomaloskop- und ERG-Befunde normal*.

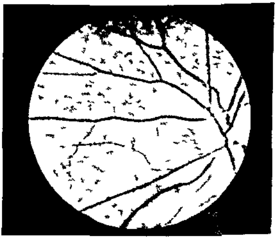


Abb. 3

Chorioideremie im Frühstadium. Be. H., 8 J., männlich. Visus re./li. 5/4. Gesichtsfeldaussengrenzen am Maggiore-Perimeter beidseits mit der 1 mm Marke 20 Grad konzentrisch eingeschränkt. Juveniler Fundus mit tüpfligen Pigmentierungen und Depigmentierungen. Papille und Netzhautgefässe normal.

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* Die ERG-Untersuchungen wurden in dankenswerter Weise an der Augenklinik der Karl-Marx-Universität Leipzig durchgeführt.



Abb 4

Übertragerin bei Chorioideremie Be G 7 J weiblich keine funktionellen Ausfalle Man beachte die Ähnlichkeit des ophthalmoskopischen Bildes zu dem des Bruders (Abb 3) im Fruhstadium der Erkrankung

ɔ Ro N Nr 7591/71 10 Jahre alt Visus rechts/links 5/5 Gesichtsfeldaussengrenzen am Maggiore Perimeter mit der 1 mm Marke 10–15 Grad konzentrisch eingeschrankt Dunkeladaptationskurve am Registrieradaptometer nach Hartinger pathologisch (nach 1 Min Endschwelle lg E = 3 5 nach 40 Min lg E = 4) Anomaloskop Untersuchung rechts links angenommene Gleichung gegenuber Normalgleichung des Tages nach grun verschoben Elektroretinogramm im Normbereich*

Auch unter Berucksichtigung der Schwierigkeit kindliche Angaben zu verwerten und zu interpretieren lassen sich schon beginnende funktionelle Storungen eindeutig nachweisen Von Interesse wird das Ergebnis der Kontrolluntersuchungen in den nachsten Jahren sein Unsere Befunde stimmen mit den aus der Literatur bekannten uberein wonach im Initialstadium keine Ausfalle zu finden sein sollen wahrend in den spateren Anfangsstadien solche zu finden sind (Kurstjens u a)

Eine sehr empfindliche Untersuchungsmethode scheint die Prufung der Unterschiedsempfindlichkeit fur Farbtone am Spektralfarbenmischapparat zu sein Fruhzeitig soll es nach Jaeger und Grutzner zu einer Verschiebung des Maximums der Unterschiedsempfindlichkeit fur blaue und grune Farbtone kommen Der Grad der Verschiebung soll ein Mass fur das Fortschreiten der Erkrankung sein Die Unterschiedsempfindlichkeit fur gelb orange Farbtone bleibt dagegen langer erhalten wodurch unter Umstanden regelrechte Angaben bei der Untersuchung am Nagel schen Anomaloskop gemacht werden

Selbstverstandlich bietet die EKG Auswertung ein wichtiges Hilfsmittel zur Verlaufskontrolle In der Literatur fehlen hierzu noch genugend Angaben uber

Pigmentierungen und Depigmentierungen zu sehen. In der Tiefe waren vereinzelte Aderhautgefässe zu erkennen, die Netzhautgefasse waren normal. Bei allen untersuchten Jungen waren die Sero-Reaktion auf Lues, Toxoplasmose, Listeriose und Bruzellose negativ.

Funktionell fanden sich im einzelnen:

1. Ra. St. Nr. 9928/71, 5 Jahre alt. Visus rechts – 7,5 s = 5/35, 1/8 (Pfluger Haken), links 5/7 (Pfluger Haken). Gesichtsfeldbestimmung und Anomaloskop-Untersuchung keine verwertbaren Angaben.

2. Ra. Th. Nr. 9927/71, 7 Jahre alt. Visus rechts/links 5/4. Ergebnisse der Gesichtsfeldbestimmung, Anomaloskop-Untersuchung und Dunkeladaptation regelrecht.

3. Ro. B. Nr. 7592/71, 6 Jahre alt. Visus rechts – 1,25 s + 0,5 cyl. A 90° = 5/4, links – 1,25 s + 0,5 cyl. A 90° = 5/4. Gesichtsfeldaussengrenzen am Maggiore-Perimeter mit der 1 mm Marke auch nach mehrfachen Kontrollen 15–20 Grad konzentrisch eingeschrankt. Ergebnisse der Dunkeladaptation und Anomaloskop-Untersuchung regelrecht.

4. Be. H. Nr. 7595/71, 8 Jahre alt (Abb. 3). Visus rechts/links 5/4. Gesichtsfeldaussengrenzen am Maggiore-Perimeter beiderseits mit 1 mm Marke bei mehrfachen Kontrollen 20 Grad konzentrisch eingeschrankt. Dunkeladaptationskurve, Anomaloskop- und ERG-Befunde normal*.

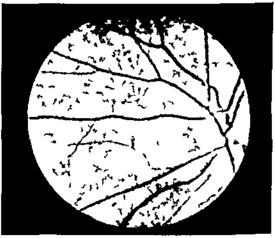


Abb. 3

Chorioideremie im Fruhstadium. Be. H., 8 J., mannlich. Visus re./li. 5/4. Gesichtsfeldaussengrenzen am Maggiore-Perimeter beidseits mit der 1 mm Marke 20 Grad konzentrisch eingeschrankt. Juveniler Fundus mit tupfligen Pigmentierungen und Depigmentierungen. Papille und Netzhautgefasse normal.

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* Die ERG-Untersuchungen wurden in dankenswerter Weise an der Augenklinik der Karl-Marx-Universitat Leipzig durchgefuhrt.



Abb 4

Übertragerin bei Chorioideremie Be G , J weiblich keine funktionellen Ausfalle Man beachte die Ähnlichkeit des ophthalmoskopischen Bildes zu dem des Bruders (Abb 3) im Fruhstadium der Erkrankung

5 Ro N Nr 7591/71 10 Jahre alt Visus rechts/links 5/5 Gesichtsfeldaussengrenzen am Maggiore Perimeter mit der 1 mm Marke 10–15 Grad konzentrisch eingeschrankt Dunkeladaptationskurve am Registrieradaptometer nach Hartinger pathologisch (nach 19 Min Endschwelle lg E = 3 5 nach 40 Min lg E = 4) Anomaloskop Untersuchung rechts links angenommene Gleichung gegenuber Normalgleichung des Tages nach grun verschoben. Elektroretinogramm im Normbereich

Auch unter Berucksichtigung der Schwierigkeit kindliche Angaben zu verwerten und zu interpretieren lassen sich schon beginnende funktionelle Storungen eindeutig nachweisen Von Interesse wird das Ergebnis der Kontrolluntersuchungen in den nachsten Jahren sein Unsere Befunde stimmen mit den aus der Literatur bekannten uberein wonach im Initialstadium keine Ausfalle zu finden sein sollen wahrend in den spateren Anfangsstadien solche zu finden sind (Kurstjens u a)

Eine sehr empfindliche Untersuchungsmethode scheint die Prufung der Unterschiedsempfindlichkeit fur Farbtone am Spektralfarbenmischapparat zu sein Fruhzeitig soll es nach Jaeger und Grutzner zu einer Verschiebung des Maximums der Unterschiedsempfindlichkeit fur blaue und grune Farbtone kommen Der Grad der Verschiebung soll ein Mass fur das Fortschreiten der Erkrankung sein Die Unterschiedsempfindlichkeit fur gelb orange Farbtone bleibt dagegen langer erhalten wodurch unter Umstanden regelrechte Angaben bei der Untersuchung am Nagel schen Anomaloskop gemacht werden

Selbstverstandlich bietet die ERG Auswertung ein wichtiges Hilfsmittel zur Verlaufskontrolle In der Literatur fehlen hierzu noch genugend Angaben uber

die Frühstadien der Ch. (Bounds und Johnston, Pameyer u. Mitarb., Jacobson und Stevens).

Unsere heterozygoten *Überträgerinnen* zeigten ähnliche ophthalmoskopische Bilder wie die Jugendlichen im Frühstadium.

Funktionell fanden wir keine Ausfälle. Die Überträgerinnen bieten demnach das Bild einer »forme fruste« (Abb. 4). Interessant ist, dass Kurstjens, Krill, Fraser und Friedmann, Harris und Miller in den letzten Jahren auch bei heterozygoten Frauen das Vollbild der Erkrankung mit funktionellen Ausfällen gefunden haben. Dafür gibt es bis jetzt keine Erklärung. Chromosomen-Inaktivierungen werden ebenso wie variable Genwirkungen diskutiert.

Chromosomenuntersuchungen haben wir bei 9 Patienten durchgeführt. Wie zu erwarten und in Übereinstimmung mit den wenigen bislang vorliegenden Einzelbeobachtungen von Fraser und Friedmann, Rubin, Fishman und McKay wurden keine strukturellen oder numerischen Aberrationen nachgewiesen. Die Abb. 5 zeigt ein normales Karyogramm bei dem erkrankten Patienten.

Das Krankheitsbild der Chorioideremie ist fest umrissen, bietet aber noch viele ungelöste Probleme. Erst wenn es gelingt, in zunehmendem Umfang Erkrankte im Frühstadium und Überträgerinnen zu erfassen und mit fluorescenzangiografischen, histologischen, biochemischen und anderen Methoden zu unter-

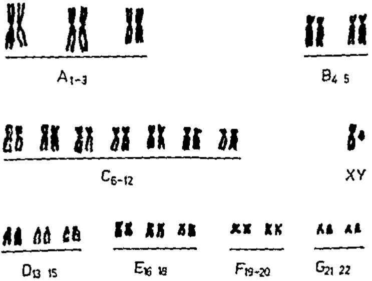


Abb. 5
Karyogramm eines an Chorioideremie erkrankten Mannes. Keine strukturellen und numerischen Aberrationen

suchen wird es moglich werden die Atiologie und die pathogenetischen Probleme weiter aufzuklaren

3 *Familienberatung* Der in Abb 1 wiedergegebene Stammbaum zeigt besonders eindrucksvoll welche Bedeutung der genetischen Familienberatung bei emessen werden muss und welche Moglichkeiten aus der Zusammenarbeit des Mediziners mit dem Genetiker fur die belastete Familie erwachsen In der von uns untersuchten Sippe besteht eine recht traurige Bilanz die aber durchaus hatte vermieden werden konnen ware der Patient bereits vor 15 Jahren in die Sprechstunde und zur genetischen Beratung gekommen Zu diesem Zeitpunkt waren die Enkelkinder (3 Generation) noch nicht geboren und aufgrund unserer Kenntnisse uber Krankheitsverlauf und Vererbungsmodus hatte die genetische Familienberatung sicherlich zu einer wesentlich gunstigeren Situation bei etragen

Da es sich um ein X chromosomal gebundenes Leiden mit intermediarem Erbgang handelt sind die belasteten Manner hemizygot und zeigen das Vollbild der Erkrankung Entsprechend den Erbgesetzen wird das X Chromosom des Vaters den Tochtern und das Y Chromosom den Sohnen vererbt Bezogen auf unseren Stammbaum und auch in Übereinstimmung mit klinischen Befunden bedeutet dies dass zwangslaufig in der 2 Generation alle Tochter heterozygote Tragerinnen sind die Sohne dagegen gesund Deshalb hatte spatestens z Z der Eheschliessung der Tochter eine Aufklarung und Beratung erfolgen mussen Erwartungsgemass sind ihre Nachkommen zu 50 % genetisch bel s et Dieses hohe Risiko und der nicht korrigierbare Phanotyp bei den hemizygoten Knaben sprechen gegen eine Nachkommenschaft dieser Frauen Unsere Aufgabe sehen wir jetzt in einer standigen Betreuung der Kinder sowie in einer volligen Aufklarung der Eltern Dabei ergeben sich nachfolgende Gesichtspunkte

1 Berufsberatung der hemizygoten Knaben

2 Standiger Kontakt mit den Kindern uber deren Eltern genetische Beratung der hemizygoten Knaben und heterozygoten Madchen zu einem angemessenen Zeitpunkt

3 Da gegenwartig noch keine Moglichkeit besteht bei Personen mit Erbleiden einen entsprechenden Vermerk im Ausweis vorzunehmen sind auch die Eltern dieser Kinder zu beraten und aufzuklaren Dadurch kann bei einem Arztwechsel auf das Erbleiden und auf die Konsequenzen hingewiesen werden

4 In jeder Klinik sollte eine separate Kartei fur jene genetischen Falle angelegt werden bei denen eine genetische Beratung aus eugenischer Sicht

angezeigt ist Nach Jahrgängen geordnet besteht die Moglichkeit die Patienten *im heiratsfähigen Alter zu bestellen und genetisch zu beraten*

Mit der hier vorgestellten Problematik soll auch von der Seite des Ophthal mologen darauf hingedeutet werden dass in zunehmendem Masse genetische Fragestellungen und Aspekte an Bedeutung gewinnen Vielmehr als bischer sollte in der augenärztlichen Sprechstunde zunächst an ein hereditäres Leiden gedacht und die Diagnose exakt gestellt werden Nur allzu oft beschrankt sich die Behandlung auf den Phänotyp Die erbliche Grundlage der Genotyp als pri märe Ursache bleibt hingegen unberucksichtigt und kann bei weiteren Nach kommen erneut manifest werden Sofern aufgrund der gestellten Diagnosen eine genetische Ursache in Betracht kommt bzw sich aus der Stammbaum analyse ergibt muss der Vererbungsmodus geklart werden und eine genetische Beratung für alle infrage kommenden Sippenangehörigen erfolgen Entschei dend für die einzuleitenden Massnahmen sind u a folgende Gesichtspunkte

1 Art der Genwirkung dominant/rezessiv geschlechtsgebunden

2 Bei rezessiver Vererbung die Haufigkeit des Allels in der Population und damit die Wahrscheinlichkeit dass 2 heterozygote Trager zusammentreffen

3 Schweregrad der Erkrankung

4 Evtl Beeinflussung einer latenten Erkrankungsform durch exogene oder endogene Noxen

Eine wesentlich Aufgabe wird in der genetischen Aus und Weiterbildung des Mediziners sowie in der Integration der Humangenetik in die medizinische Betreuung gesehen Genetische Familienberatung ist aber nur *eine* Möglichkeit wie auf dem Wege der negativen Eugenik das Auftreten erbkranken Nach wuchses eingeschränkt bzw verhindert werden kann

Eine zweite und nicht weniger bedeutungsvolle Aufgabe ist in der genetischen Aufklärung der Bevolkerung zu sehen bei der das Verstehen der Problematik und das Verstandnis fur das Anliegen vordergrundig sind

Gegenwärtig beschranken sich die Massnahmen der negativen Eugenik auf die genetische Beratung der Familien Sieht man von Einzelfallen ab so bleibt dies dem behandelnden Arzt vorbehalten Wir mussen uns aber bewusst bleiben dass auf diesem Wege und mit den gegenwartigen Moglichkeiten weder ein durchgreifender Erfolg noch ein »Erbgesundheitswesen« geschaffen werden kann Hierzu sind weitere Massnahmen erforderlich von denen nur einige genannt werden sollen wie z B Meldepflicht fur alle Erbkrankheiten Erb gesundheitspass genetischer Beratungsdienst und Errichtung zytogenetischer Untersuchungslaboratorien

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PAPILLOEDEMA ASSOCIATED WITH RUPTURED INTRACRANIAL ANEURYSMS

BY

J A FAHMY

Among 19[illegible] patients with intracranial aneurysms 3[illegible] had papilloedema This corresponds to 16 % (99 % confidence limits 10–[illegible]4) The papilloedema did not vary significantly by sex age or site of aneurysm It was unilateral in [illegible] cases corresponding to the side of the aneurysm or haematoma in 6 cases Papillary prominence was slight and most often was accompanied by varying degrees of haemorrhage It was not possible to demonstrate a relationship between the vascular hypertension or cerebral vascular sclerosis and the occurrence of papilloedema nor was there any correlation with the intracranial hypertension as judged by the occurrence of cerebral haematomas around the aneurysms or intraventricular haemorrhages and arachnoid adhesions on the one hand and papilloedema on the other The papilloedema is presumably due to the subarachnoid haemorrhages in the sheaths of the optic nerves The haemorrhage compromises the central retinal vein in its course through the subarachnoid space and thereby causes stasis of the venous outflow from the [illegible] This phenomenon could be demonstrated histopathologically and will be described in more detail in a subsequent paper The operative risk was found to be increased in patients with papilloedema

Key words papilloedema – intracranial aneurysms – subarachnoid haemorrhage – operative risk

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papilloedema (18 %) (Fig 1) Fig 2 illustrates the age distribution of the papilloedema There was no significant difference in the occurrence of papil loedema by site sex or age ($p > 0.1$)

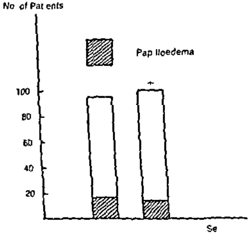


Fig 1
Sex d strit ut on of 3? patients with papilloedema among 19ɔ cases of intracran al aneurysms

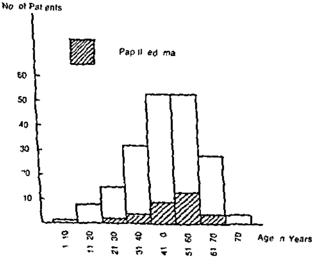


Fig 2
Age distr bution of 3_ patients with papilloedema related to that of 163 without

The reported incidence of papilloedema in intracranial aneurysms has varied from 10% (Dandy 1944) to 24% (Krayenbühl & Yasargil 1958) The papilloedema has been described as moderate (Manschot 1944 Walsh & Hoyt 1969) and when fully developed is frequently accompanied by haemorrhage (Manschot 1944) Tureen (1938) found no relationship between the prominence of the disc and the severity of the retinal haemorrhages According to Uhthoff (1901) the papilloedema may develop in a matter of hours This was confirmed by Tureen who observed four cases developing in the course of two hours Hamby (1952) had not seen papilloedema appear until the seventh day

The object of the present study was to (1) establish the incidence of papilloedema in intracranial aneurysm (2) describe the morphology of the papilloedema (3) determine the time elapsing from the rupture of the aneurysm until the appearance of papilloedema viz the "time of development (4) study some factors of possible pathogenetic significance and lastly (5) assess the prognostic value of papilloedema

Material and Methods

The material comprises 195 patients admitted as cases of intracranial aneurysm during the period 1 4 1959 to 31 3 1970 (11 years) to Neurosurgical Department S Municipal Hospital Århus The diagnosis was purely anatomical i e established either at operation (144 cases) or at autopsy (51) or both (26 cases) Out of the original series of 221 consecutive patients the following 26 were excluded 9 patients who died before the operation and were not autopsied and 4 patients who were discharged without operation (In these 13 cases the aneurysms were demonstrated by angiography but since the diagnosis cannot be based solely on the angiography (Knudsen & Fahmy 1971) these patients were excluded) Six patients had co existing angioma 2 meningioma and 1 cerebral metastasis In 3 patients with a history of trauma it could not be decided with certainty whether the aneurysm was congenital or traumatic One patient with a typical history and angiographic findings underwent operation without any aneurysm being found

Statistical calculations Chi square significance test In calculations on 2 × 2 tables Yate s correction was used

Results

Incidence

Among the 195 patients 32 had papilloedema (16 %) Table I gives the distribution of papilloedema by site of aneurysm Out of the 195 patients 100 were women and of these 15 had papilloedema (15 %) Among the 95 males 17 had

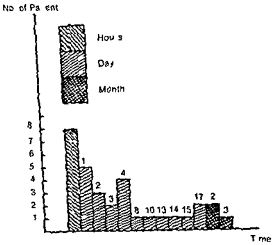


Fig 4

Time intervals between rupture of aneurysms and ophthalmologic examination in 32 patients with papilloedema

11 cases ⁹ patients had a prominence of 0 5 and 10 of 1 dioptre 9 had a prominence exceeding 1 and two exceeded 2 dioptres

In ⁹ instances the papilloedema was associated with retinal *haemorrhage* mild (grade I) in 11 cases more severe but still at the retinal level (grade II) in another 11 and large preretinal or vitreous (grade III) in 5 patients

Fig 3 shows clearly that no correlation exists between the prominence of the dis and the severity of the retinal haemorrhages

Time of development

This is defined as the interval between the rupture of the aneurysm and the appearance of papilloedema In the 8 patients examined a few hours after the rupture there was hyperaemia of the disc developing in 3 of the cases within hours to a prominence of 1 dioptre The other patients (Fig 4) were not admitted and examined until 24 hours – 3 months *after the attack* so that an accurate interval could not be demonstrated

Relationship to some factors of possible pathogenetic significance

The material was divided into 2 groups 32 patients with papilloedema and 163 patients without (Table II) *Arterial hypertension* (previously diagnosed) was present in 8 (25 %) of the former group and in 19 (12 %) of the latter this difference is not significant *Cerebral arteriosclerosis* was demonstrable by

Table I

Distribution of papilloedema in intracranial aneurysms of different sites

	No of patients	Papilloedema
Anterior cerebral artery	13	3
Anterior communicating artery	61	13
Internal carotid artery	63	9
Middle cerebral artery	52	5
Basilar artery	3	–
Ophthalmic artery	2	2
Primitive trigeminal artery	1	–
Total	195	32

Morphology

The papilloedema was unilateral in 7 cases In 6 of these cases the side of the papilloedema corresponded to that of the aneurysm or haematoma In 24 cases the papilloedema was bilateral In one of these cases this could not be determined because of unilateral corneal opacity Among the 24 patients with bilateral papilloedema 19 showed equal prominence whereas in 4 cases there was a difference of 0 5–1 dioptre and in one case of 2 dioptres As regards prominence (Fig 3) the discs were hyperaemic and without prominence in

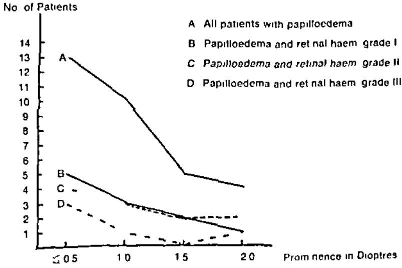


Fig 3

Correlation between prominence of disc and grade of retinal haemorrhage

Discussion

Papilloedema occurs in 16% of all patients with ruptured intracranial aneurysms. The variation in the reported incidence (Table IV) is within 99% confidence limits 10–24% ($p < 0.01$) explicable as a random sample variation.

Tureen's (1939) finding of no relationship between prominence of the disc and the severity of the retinal haemorrhages is supported by the present investigation and explicable by the two signs being independent of each other. Whereas retinal haemorrhages of different severity occur simultaneously with the rupture of the aneurysm, papilloedema does not appear until hours later. This was observed in some patients admitted a short time after the onset. An accurate analysis of the time of development of papilloedema is not practicable because many patients are not admitted until days, sometimes months, after the aneurysmal rupture. Therefore the claim concerning a late development of the papilloedema can only be taken with some reserve (Hamby 1952, Walsh & Hoyt 1969).

Griffith et al. (1938) found a relationship between arterial hypertension, intraventricular haemorrhages or large aneurysms acting as neoplastic masses and the occurrence of papilloedema in intracranial aneurysms. The present study showed no relationship between the vascular hypertension and the occurrence of papilloedema or to cerebral haematomas around the aneurysms or intraventricular haemorrhage, both of which are usually accompanied by increased intracranial pressure and papilloedema. Walsh & Hoyt (1969) believed that arachnoid adhesions to the base of the brain – blocking the flow of cerebrospinal fluid and thereby raising the intracranial pressure – may be an important pathogenetic factor in papilloedema.

This contention could also not be confirmed in the study of the present ma

Table IV
Incidence of papilloedema in intracranial aneurysms

Authors	Aneurysms	Papilloedema %
Richardson & Hyland (1941)	118	1[illegible]
Dandy (1944)	108	10
Hamby (19[illegible])	130	14
Timberlake & Kubik (1959)	250	19
Krayenbühl & Yasargil (19[illegible])	130	24
Present cases	195	16

Table II
Papilloedema in relation to some factors of possible pathogenetic significance

Factors	Intracranial aneurysms		
	Papilloedema (32 pts)	No papilloedema (163 pts)	Total
Arterial hypertension	8	19	27
Cerebral vascular sclerosis	14	59	73
Intracerebral haematoma or intraventricular haemorrhage	11	53	64
Recurrent aneurysmal haemorrhages	10	46	56

angiography in a total of 73 patients 14 (48 %) of the former group and in 59 of the latter (36 %) this difference is also not significant *Intracranial haematoma or intraventricular haemorrhage* was present in 11 patients (34 %) with papilloedema and in 53 (33 %) without

Recurrent aneurysmal haemorrhage had occurred in 56 patients Ten exhibited papilloedema (31 %) whereas 46 did not (28 %) a difference which *is not significant*

Prognostic role

A total of 144 patients underwent operation From Table III it is apparent that only 28 out of 122 (23 %) of the operated patients without papilloedema died whereas 11 out of 22 patients (50 %) with papilloedema died This difference is significant ($p < 0\ 05$)

Table III
Clinical course in 32 patients with papilloedema compared with that in 163 patients without

Patients		Surviving	Dead	Total
Operated	Papilloedema	11	11	22
	No papilloedema	94	28	122
Not operated	Papilloedema	0	10	10
	No papilloedema	0	41	41
		105	90	195

Discussion

Papilloedema occurs in 16 % of all patients with ruptured intracranial aneurysms The variation in the reported incidence (Table IV) is within 99 % confidence limits 10-24 % ($p < 0.01$) explicable as a random sample variation

Tureen s (1939) finding of no relationship between prominence of the disc and the severity of the retinal haemorrhages is supported by the present investi ation and explicable by the two signs being independent of each other Whereas retinal haemorrhages of different severity occur simultaneously with the rupture of the aneurysm papilloedema does not appear until hours later This was observed in some patients admitted a short time after the onset An accurate analysis of the time of development of papilloedema is not practicable because many patients are not admitted until days sometimes months after the aneurysmal rupture Therefore the claim concerning a late development of the papilloedema can only be taken with some reserve (Hamby 1952 Walsh & Hoyt 1969)

Griffith et al (1938) found a relationship between arterial hypertension intraventricular haemorrhages or large aneurysms acting as neoplastic masses and the occurrence of papilloedema in intracranial aneurysms The present study showed no relationship between the vascular hypertension and the occurrence of papilloedema or to cerebral haematomas around the aneurysms or intraventricular haemorrhage both of which are usually accompanied by increased intracranial pressure and papilloedema Walsh & Hoyt (1969) believed that arachnoid adhesions to the base of the brain – blocking the flow of cerebrospinal fluid and thereby raising the intracranial pressure – may be an important pathogenetic factor in papilloedema

This contention could also not be confirmed in the study of the present ma

Table IV
Incidence of papilloedema in intracranial aneurysms

Authors	Aneurysms	Papilloedema %
Richardson & Hyland (1941)	118	12
Dandy (1944)	108	10
Hamby (19[illegible])	130	14
Timberlake & Kubik (19[illegible])	280	19
Krayenbuhl & Yasargil (19[illegible])	136	24
Present cases	195	16



Fig. 5 and 6
Subarachnoid haemorrhage in the optic nerve of a 45 year old patient who died from ruptured aneurysm on the anterior communicating artery

terial of patients with recurrent aneurysmal haemorrhages Moreover as al ready mentioned the papilloedema often occurs within hours of the haemor rha e i e long before the adhesions have developed

The presumably lacking relationship between the intracranial pressure and the occurrence of papilloedema further confirmed by the 7 unilateral cases renders it more likely that the papilloedema arises in consequence of the subarachnoid haemorrhages in the optic sheaths The haemorrhage compresses the cen ral retinal vein in its course through the subarachnoid space and there by gives rise to congestion in the venous outflow from the disc This phenom enon could be demonstrated histopathologically in several cases and will be described in a subsequent paper

As the operative risk was found to be increased in patients with papilloedema it is justified and desirable to assign to this category of patients a central po sition in future risk grouping of patients with ruptured intracranial aneurysms

Acknowledgement

In the statistical cal ulations the author was guided by H R Wulff M D Gentofte Hospital Copenhagen Adviser in Biostatistics to the Danish Medical Research Council

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EFFECT OF HYALURONIDASE ON THE OCULAR PENETRANCE OF AMPICILLIN

BY

JOHN V THOMAS

It has been suggested that hyaluronidase when given subconjunctivally may increase the penetration of antibiotics such as penicillin into ocular fluids and tissues Its effect on a synthetic penicillin viz ampicillin has been evaluated here Forty eight New Zealand white rabbits were divided into two numerically equal groups Group I received 62 5 mg ampicillin and Group II received 62 5 mg ampicillin + 30 T R U of hyaluronidase All injections were made subconjunctivally Ampicillin levels in cornea aqueous vitreous and optic nerve were determined The results suggest that hyaluronidase has no effect in increasing the intraocular penetration of antibiotics

Key words hyaluronidase – ampicillin – ocular penetrance

Studies on the effectiveness of the depolymerizing enzyme hyaluronidase as a spreading absorption aiding agent in ocular fluids and tissues have yielded variable results since its discovery (Meyer Dubos & Smyth 1936) It has been demonstrated that hyaluronidase does not increase the intraocular penetration of procaine following subconjunctival injection (Schlegal & Swan 1954) It does not have an enhancing effect upon the corneal penetration of dimercaprol (Harris & Cohen 1953) or on the diffusion of inorganic phosphate into the vitreous body (Christiansson 1955) It does not facilitate aqueous humor pene

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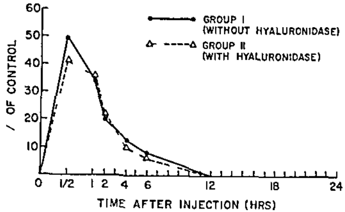


Fig 1

Ampicillin activity in aqueous humor with and without hyaluronidase

tration of the antibiotic lincomycin or of mannitol when injected subconjunctivally (Melikian Nowakowski Boyle & Leopold 1971)

However it has been experimentally demonstrated that hyaluronidase increases the penetration of fluorescein dye into the anterior chamber (Capolongo 1950) In addition it has been suggested by many authors that the absorption of antiobiotics such as penicillin or mydriatics such as atropine may be enhanced by the enzyme (Lebensohn 1950 Dubois Poulsen Loisillier Cochet & Descamps 1952 Sedan 1952 Junceda 1953 Selfa 1954)

As hyaluronidase reportedly increases the intraocular penetration of penicillin it was considered important to evaluate its effect when given subconjunctivally on the ocular penetrance of ampicillin a widely used synthetic penicillin with broad spectrum antibacterial activity It is the purpose of this paper to report these results

Materials and Methods

Forty eight New Zealand white rabbits weighing from four to six pounds each were used as the experimental animals They were divided into two numerically equal groups and anesthetized with 25 mg/kg sodium pentobarbital given intravenously Each Group I animal received a single subconjunctival injection of freshly prepared sodium ampicillin dissolved in sterile saline in a concentration of 62 5 mg/0 45 ml Each Group II animal received a single subconjunctival injection of 62 5 mg sodium ampicillin + 30 T R U (Turbidity Reducing Units) of hyaluronidase dissolved in 0 45 ml of sterile saline Only

one eye of each animal was used and all injections were made in the superior temporal quadrant

At each of eight predetermined times after subconjunctival injection three rabbits from each group were sacrificed with intravenous pentobarbital The disk tissue method was used to assay for antibiotic levels in cornea aqueous humor vitreous humor and optic nerve (Crawford 1969) After the animal was sacrificed the eye was immediately irrigated with sterile saline With a 5 mm diameter Castroviejo trephine a nonpenetrating corneal incision 0 3 mm deep was made and a lamellar keratectomy done Then the anterior chamber was entered with a 27 gauge needle inserted through an intact area of cornea and aqueous humor was withdrawn

Enucleation was then carried out leaving the longest piece of optic nerve possible The eye was flushed with saline and clean instruments were used to free the optic nerve from its adventitia A section of nerve approximately 1 mm long was taken Vitreous humor was obtained with a 10 gauge needle inserted through a clean dry piece of sclera posterior to the equator

Cornea and optic nerve were placed directly on a human blood agar plate previously streaked with an incubated broth suspension of non hemolytic coagulase positive Staphylococcus aureus (American Type Culture Collection No 25923) The broth suspension had been visually calibrated with a barium sulfate turbidity standard prepared by adding 0 5 ml of 1 % barium chloride solution to 99 5 ml of 1 % sulfuric acid

The samples of aqueous and vitreous were used to saturate 6 mm disks made of No 40 Whatman filter paper The disks were then placed on similarly streaked blood agar plates In addition three control disks were prepared for each animal One was saturated with ampicillin in the concentration used for injection the other with ampicillin and hyaluronidase and the third disk with 30 TRU hyaluronidase alone After incubating the blood agar plates for 24 hours at 37 C zones of inhibition were measured Percent of control was calculated by dividing the average total diameter of inhibition of each sample less 6 mm (the disk diameter) by the average total diameter of inhibition of the control less 6 mm

Results

Levels of ampicillin activity in aqueous cornea vitreous and optic nerve after subconjunctival injection of the antibiotic with and without hyaluronidase are summarized (Figs 1–4) On the blood agar plates streaked with *Staph aureus* organisms the control disks saturated with ampicillin or ampicillin and hyaluronidase were found to have identical zones of inhibition The control disk

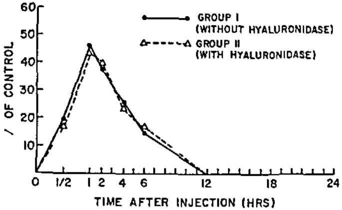


Fig 2

Ampicillin activity in cornea with and without hyaluronidase

saturated with hyaluronidase alone was found not to have any antibacterial activity

In Group I animals the aqueous levels of ampicillin are seen to rise rapidly and peak at 30 minutes (Fig 1) No detectable levels of the antibiotic are present at 12 hours In Group II animals hyaluronidase does not seem to have any effect in increasing the penetration of ampicillin into aqueous humor

Maximal levels of ampicillin are seen in the cornea 1 hour after subconjunctival injection (Fig 2) Twelve hours after administration of the antibiotic no ampicillin activity is present in the cornea In the presence of hyaluronidase no increased penetration of ampicillin into the cornea is noted

Antibiotic activity of the optic nerve was maximal at 2 hours (Fig 3) Vit

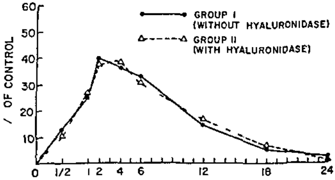


Fig 3

Ampicillin activity in optic nerve with and without hyaluronidase

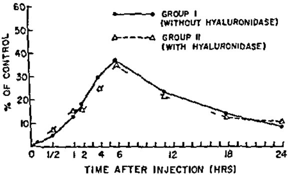


Fig 4

Ampicillin activity in vitreous humor with and without hyaluronidase

reous activity (Fig 4) is similar to that in the optic nerve and antimicrobial activity in both tissues continues longer than 24 hours after subconjunctival injection of ampicillin Hyaluronidase is seen not to increase the penetration of the antibiotic in either tissue

In Group I animals the ampicillin levels obtained are similar to those of other investigators (Crawford & McPherson 1971) In Group II animals the enzyme hyaluronidase does not increase the levels of ampicillin in any of the fluids or tissues assayed

Discussion

The enzyme hyaluronidase has been of interest because of its ability to de polymerize and hydrolyze hyaluronic acid the acid mucopolysaccharide which in loose combination with proteins serves to act as an intercellular cement Clinically it has been used to increase the effect of local anesthetics when given in a retrobulbar fashion prior to intraocular surgery

Though the exact mechanism is unclear it has been suggested in the litera ture that the penetration of penicillin into ocular tissues might be increased in the presence of hyaluronidase Therefore the possibility that a similar anti biotic would be affected in a like manner is enticing However this study fails to substantiate this hope

Variability in the results obtained by different investigators using hyalu ronidase to increase ocular penetration of various drugs may be due to the nature of the drugs used or to the techniques employed

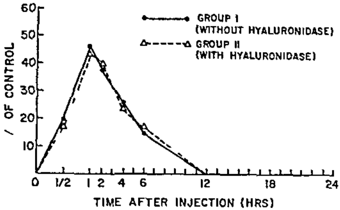


Fig 2

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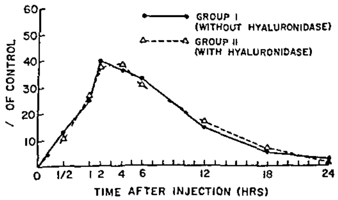


Fig 3

Ampicillin activity in optic nerve with and without hyaluronidase

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METHOD OF TESTING DYES FOR VITAL STAINING OF CORNEA AND CONJUNCTIVA

BY

M S NORN

Lines are given for testing dyes intended for use in vital staining of the cornea and conjunctiva especially dyes having properties different from those of the well known fluorescein and rose bengal

A priority list for dye testing has been made comprising six items

1) Water solubility (a 1 % solution in non irritant vehicle is desirable)

2) Toxicity tests (dyes should cause no smarting pain nor effect permanent tatooing)

3) Microscopy of the mucous thread in the inferior conjunctival fornix (possible staining of mucous fibrils debris in the mucous thread vacuoles different cell types nucleus cytoplasm mitochondria etc)

4) Clinical vital staining of normal eyes keratitis etc

5) Double staining with a known vital stain (successive staining or use of a dye mixture) of a clinical material examined in slit lamp or microscope

6) Conclusion and entering in a diagram of the vital stains tested so far

Key words vital staining – procedure – double staining – dye mixture – fluorescein – rose bengal – lissamine green

Fluorescein is usually employed for vital staining of the cornea and the conjunctiva Fluorescein penetrates through defects if *present in the* surface epithelium thus staining these defects Rose bengal can also be used this dye

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of the dye solution should be close to the neutral point (pH between about 5 and 9)

The dye solution can be tested initially by leaving a drop of the dye on the tongue (taste) This is followed by instillation of additionally diluted solution into the conjunctival sac, touching of the conjunctiva with a fraction of a drop on a glass rod and finally proper instillation into the conjunctival sac

Some dyes may cause permanent discoloration Careful observation must be made for this phenomenon in the initial tests (how soon does the dye disappear from the tongue?) and attention must also be given to it in the first clinical tests (careful examination in the slit lamp)

Splitting of the nasolacrimal duct causes injury of the connective tissue through the thin epithelium A subsequently instilled vital stain may then reach connective tissue and thus possibly effect connective tissue tatooing (alcian blue for instance)

3 MICROSCOPY OF MUCOUS THREAD

The vital stained mucous thread in the inferior conjunctival fornix can be cautiously removed by getting it to adhere to the ends of two small wooden sticks and transferring it to a slide One drop of physiological saline is added and the specimen is covered by a cover slip Microscopy will now disclose which parts of the mucous thread become vital stained The specimen contains mucous fibrils cells and vacuoles with detritus The cells generally comprise both epithelial cells and leucocytes occasionally also lymphocytes Which cells become stained? Do most cells remain unstained? Are the nuclei stained more intensely than cytoplasm or are coloured granules present in cytoplasm?

Like rose bengal most dyes stain both mucous fibrils and cells This is a disadvantage because mucus is a normal phenomenon whereas stained cells are found mainly in pathological processes

At this stage of the investigation the relatively few tests will have clarified whether the dye is fit for vital staining (items 1 and 2) and which structures the dye stains The question of whether the properties of the dye correspond to those of rose bengal or are totally different can also be settled

4 CLINICAL TESTS

The clinical tests comprise normal and pathological cases From a clinical aspect it would be convenient if normal structures remained unstained while pathological structures were distinctly stained Acidophilic dyes (e g rose

staining damaged epithelial cells A mixture of these two dyes is even more useful Defects are stained yellow by fluorescein and degenerate cells red by rose bengal (Norn 1972)

New dyes employed within histology further advances with enzyme research and an improved knowledge of the ultrastructure of the cell can doubtless stimulate us to experiment with new dyestuffs for vital staining of cornea and conjunctiva

This theory prompted me to prepare a dye mixture tetrazolium and alcian blue where tetrazolium stains enzyme containing mitochondria in the cyto plasm of the cell while alcian blue stains mucus only

At present I am studying the properties of lissamine green Congo red and neutral red

To facilitate other investigations into the properties of potential vital stains in the staining of cornea and conjunctiva I may lay down rules for such investigations based on my own experience (trypan blue methylene blue bromothymol blue etc (Norn 1972))

Testing of a potential vital stain comprises the following six items 1) water solubility 2) toxicity 3) microscopy of mucous thread 4) clinical tests 5) double staining 6) conclusion

Improvisation is however also required in the individual case

1 WATER SOLUBILITY

The dye intended for vital staining of the external eye should be water soluble Most dyes are used in a not less than 1 % solution This excludes various dyes (e g the fat specific) Vital stains cannot be used with for instance alcohol as vehicle (too toxic to the cornea) whereas Tween and other subsidiary ma terials can improve *the water solubility*

If the dye precipitates in aqueous solution it will yield false staining of mucous fibrils undissolved dye grains being caught by mucous fibrils in the same manner as all other foreign bodies A high water solubility is therefore required for a dye to be useful for vital staining

2 TOXICITY

A vital stain should cause no smarting pain Intense smarting stimulates the lacrimation and injures the mucosa Streaming lacrimation dilutes the dye too soon while injury may give artificial staining The hydrogen ion concentration

stilled dye may stain more intensely than the primarily instilled one because the latter may have damaged the mucosa We cannot be certain that both dye drops have been instilled optimally

These sources of error can be avoided by using a mixture of the two dyes This presupposes however that the dyes do not precipitate when mixed that they preserve their specific staining properties in the mixture and that the two staining elements can be distinguished in the slit lamp

Fluorescein and rose bengal is an example of such a mixture Fluorescein stained regions are disclosed by fluorescence in cobalt filtered light while rose bengal stained regions are seen as red areas in white light

Lissamine green and rose bengal is another combination which I am studying at present Green greenish (blue?) blue and red regions are noticed in the slit lamp Red areas seen in white light are rose bengal stained The other regions are examined in light that has passed through a green filter (red free light) If the stained area disappears (is of a green colour identical with that of the green cornea and conjunctiva) the area is stained by lissamine green alone If standing out as a definitely black stained area on a green background it must have been stained by the red component rose bengal too

The direct comparison between the unknown dye and the known vital stain must be carried through in different regions (cornea bulbar conjunctiva tarsal conjunctiva Marx line plica semilunaris caruncle and mucous thread in the inferior fornix) and in different clinical states The result is noted down and sketched on a punched card

The slit lamp examination is supplemented by microscopy of the double stained mucous thread epithelial scrapings and aspirated conjunctival fluid

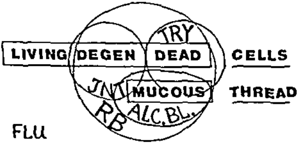


Fig 9
Vital staining of cells and mucus The diagram illustrates which structures are vital stained by rose bengal (RB) alcian blue (ALC BL) iodonitrotetrazolium (JNT) trypan blue (TRY) and fluorescein (FLU)

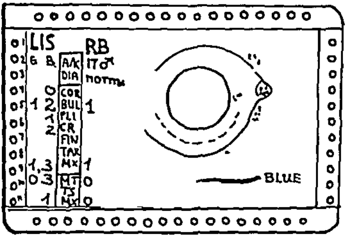


Fig 1
Punch card with results of vital staining of cornea and conjunctiva by lissamine green and rose bengal

bengal) stain Marx line in normal eyes i e a streak of the tarsal conjunctiva just behind the mouths of the meibomian glands

Pathological cases should comprise corneal erosion e g immediately after removal of foreign bodies marginal keratitis dendritic keratitis keratoconjunctivitis sicca etc

Stained areas are studied microscopically

5 DOUBLE STAINING

The same eye is stained both with the unknown dye and with a known vital stain e g rose bengal

If the unknown dye is blue for instance we may start by staining with the red rose bengal and then record the staining grade (arbitrary grading from 1 to 5 grade 1 indicating minimum staining grade 3 medium and grade 5 maximum) The result may finally be sketched (on a punched card Fig 1)

Then follows vital staining with the blue dye and the blue colour is noted down on the same punched card

It is not enough to read the result after conclusion of the double staining alone because blue stained regions possibly may consist of both a blue and a red component Blue areas may cover up red ones as the violet mixed colour may seem blue

This double staining has the following disadvantages The secondarily in

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CHANGES IN AXIAL LENGTH AND OTHER DIMENSIONS OF THE EYEBALL WITH INCREASING AGE

BY

D A LEIGHTON and A TOMLINSON

A significant reduction in axial length of the eyeball with increasing age was found when one essentially normal eye of each of 72 persons was studied ($p < 0.01$) In 53 of these subjects the horizontal diameter of the cornea also became less with increasing age ($p < 0.01$) Lens thickness became greater and anterior chamber depth less ($p < 0.001$ each) Against the rule rather than with the rule corneal astigmatism was found in old age ($p < 0.001$)

It is suggested that such a reduction in size of cornea and of the whole eyeball with increasing age would contribute to the shallowness of the anterior chamber in old age and in angle closure glaucoma

A reduction in the total circumference of the trabecular meshwork available for the escape of aqueous and also a diminution in calibre of the scleral openings concerned in uveo scleral bulk flow would also result from a reduction in size of cornea and sclera

Key words age axial length of eyeball – horizontal corneal diameter corneo scleral envelope – anterior chamber depth – trabecular meshwork ocular tension

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6 CONCLUSION

The results of the tests especially items 4 and 5 demonstrate the properties of the new vital stain The properties of the dye can now be illustrated in a diagram in which the dyes tested so far have been set out Mucus and cells are indicated in the diagram the cells classified into live cells more or less degenerate cells and dead cells (Fig 2)

The diagram allows us to foretell which dye combinations may become of clinical interest in vital staining of the cornea and conjunctiva

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conjunctivitis	2*
macular degeneration	3
anterior uveitis	2*
epiphora	1*
branch retinal vein occlusion	1*
	72

* data from the unaffected eye were included

The 72 subjects comprised 44 males and 28 females Their mean age was 43.5 years (range 19 to 82 years) and their mean refraction + 0 427 D (range + 3 00 DS to − 3 50 DS) (best sphere)

The subjects were arranged into 36 pairs matched for sex and refractive error within ± 0 75 DS but differing in age by between 56 and 24 years (mean difference 34 78 years)

Young group

Mean age 25 17 years range 19 to 51 years mean refraction + 0.368 DS range + 2 25 to − 3 50 DS

Old group

Mean age 61 83 years range 44 to 82 years mean refraction + 0 486 DS range + 3 00 to − 3 00 DS

No correlation between age and refraction was found (r = − 0 134)

The following data were recorded from one eye chosen at random or from an unaffected eye as indicated of the 72 subjects

(I) Refraction determined objectively and subjectively

(II) Horizontal and vertical corneal radius by the Zeiss keratometer

(III) Horizontal corneal diameter from a colour photograph of the anterior surface of the eye (This was measured on only 53 of the 72 subjects)

(IV) Corneal thickness by the type I attachment for the Haag Streit 900 slit lamp (This was measured on only 53 of the 72 subjects)

(V) Depth of the anterior chamber measured from the anterior surface of the cornea to the anterior surface of the lens by the type II attachment for the Haag Streit 900 slit lamp

(VI) Applanation tension recorded with the attachment for the Haag Streit 900 slit lamp

It is well known that the eyeball in old age tends to have certain characteristics the anterior chamber has become shallow (Raeder 1922) the crystalline lens is thickened (Priestley Smith 1883) and the vertical curvature of the cornea is flattened in comparison with the horizontal i e against the rule rather than "with the rule" astigmatism is found (Marin Amat 1956) These features viz a shallow anterior chamber (Rosengren 1931) and a thick lens (Aizawa 1960) have been shown to be features of angle closure glaucoma compared to the normal in persons of similar age McLenachan & Loran (1967) found that "against the rule" astigmatism was more common in patients with angle closure glaucoma than in normals

Priestley Smith (1890) found that in old people the cornea is smaller than is normal in young people and suggested that this might indicate that older eyes have a smaller volume Storey & Phillips (1971) also found a smaller horizontal corneal diameter in the old than in the young and these authors as well as Grieten & Weekers (1962) found that the cornea is smaller in angle closure glaucoma than is normal

A reduction in size of the cornea with increasing age might well be a part of a tendency for the whole corneo scleral envelope to become smaller possibly due to a reduction in the length of its constituent collagen fibres Such a trend could be of importance in the aetiology of glaucoma

Method

Axial length as well as several other measurements of the eyeball were recorded in a group of 72 subjects of widely differing age with no known family history of glaucoma The subjects comprised

University students	28
University staff	14
Patients from refraction clinic	9
Patients with	
keratoconjunctivitis sicca	3
meibomian cyst	1*
corneal abrasion	4*
Herpes zoster Ophthalmicus	1*
vitreous floater	1
traumatic hyphaema	1
suspected carotid occlusion	1*

Table I cont

Correlations between age and						
Anterior chamber depth	Lens thickness	Corneal thickness	Corneal height	Relative lens position	Axial length of scleral envelope
72	72	53	53	72	53
0 67	+ 0 839	− 0 [illegible]	− 0 100	+ 0 193	− 0 141
6 34	12 971	1 676	0 718	1 646	1 175
<0 001	<0 001	0 10<p<0 20+	0 40<p<0.50+	0 10<p<0 20+	0 90<p<0.30+

significant correlation + correlation not significant

Table II cont

Horizontal corneal radius	With the rule to against the rule corneal astigmatism	Corneal thickness	Anterior chamber depth	Lens thickness	Applanation tension mmHg
36	36	17	36	36	36
7 95	+ 0 183	0 571	3 55	3 93	15 00
1 6 5 0 007	1?4 5 0 001	47.5 0 075+	47 0 001	1 0 001	197.5 0 033
7 61	+ 0 0 [illegible]	0 553	3 14	4 3	15 75

significant correlation + correlation not significant

Table I

Correlations between age and dimensions of the eyeball in one normal eye of /2 subjects Ages ranged from 19 to 82 years refraction ranged from + 3 00 to − 3 50 DS

Correlations between age and					
Dimension in mm	Axial length	Corneal diameter	Vertical corneal radius	Horizontal corneal radius	With the rule to against the rule corneal astigmatism
Number of subjects	72	53	72	72	/2
Correlation coefficient r_s	− 0 316	− 0 325	− 0 268	− 0 535	+ 0 465
t	2 786	2 454	2 327	5 298	4 395
p	0 005<p<0 010*	0 005<p<0 010*	0 025<p<0 050*	<0 001*	<0 001*

Table II

Changes in dimensions of the eyeball with age in one normal eye of 72 subjects The 72 subjects were arranged into 36 pairs matched for sex and refractive error within ± 0 75 DS but differing in age by between 56 and 24 years (mean difference 34 78 years) The Wilcoxon Matched Pairs Signed Ranks Test (Siegel 1956) was used

Dimensions in mm		Axial length	Corneal diameter	Vertical corneal radius
Number of Matched Pairs		36	17	36
Younger member of each matched pair mean age 25 years	Mean	23 42	11 40	7 77
Difference	Wilcoxon T	185	26 5	193
	p	0 018	0 02	0 046*
Older member of each matched pair mean age 62 years	Mean	23 15	11 04	7 64

Table I cont

Correlations between age and						
Anterior chamber depth	Lens thickness	Corneal thickness	Corneal height	Relative lens position	Axial length of scleral envelope
[illegible]	[illegible]	53	53	[illegible]2	53
0 6[illegible]	+ 0 839	− 0 [illegible]	− 0 100	+ 0 193	− 0 141
6 731	1[illegible] 921	1 6[illegible]6	0 718	1 646	1 12[illegible]
<0 001	<0 001	0 10<p<0 [illegible]0	0 40<p<0 50+	0 10<p<0 [illegible]0+	0 20<p<0 30+

[illegible] significant correlation + correlation not significant

Table II cont

H[illegible]rizontal corneal radius	With the rule to against the rule corneal astigmatism	Corneal thickness	Anterior chamber depth	Lens thickness	Applanation tension mmHg
3[illegible]	36	17	36	3[illegible]	36
9	+ 0 183	0 571	3 55	3 [illegible]2	15 00
1 65 0 0[illegible]	1 [illegible]5 0 001	4[illegible]5 0 075	4 0 001	1 0 00[illegible]	19[illegible]5 *0 033*
[illegible]	+ 0 0 [illegible]	0 553	3 14	4 73	15 75

[illegible] signifi[illegible]ant correlation correlat[illegible]on not significant

Table I

Correlations between age and dimensions of the eyeball in one normal eye of 72 subjects Ages ranged from 19 to 82 years refraction ranged from + 3 00 to − 3 50 DS

	Correlations between age and				
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Correlation coefficient r_s	− 0 316	− 0 325	− 0 268	− 0 535	+ 0 465
t	2 786	2 454	2 327	5 298	4 395
p	0 005<p<0 010*	0 005<p<0 010*	0 025<p<0 050*	<0 001*	<0 001*

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	p	0 013*	0 07	0 046*
Older member of each matched pair mean age 62 years	Mean	23 15	11 04	7 64

respectively) i e the corneal curvature became steeper but this tendency was more marked in the horizontal than in the vertical radius (see Table II which shows the mean values for corneal radius in young subjects compared to old subjects) This finding was therefore consistent with the already mentioned change from with to against the rule corneal astigmatism with increasing age

COMPARISONS OF DIMENSIONS BETWEEN YOUNG AND OLD GROUP OF SUBJECTS

Table II shows statistical comparisons between the mean ocular dimensions of 36 pairs of subjects i e 36 young subjects were each matched for sex and refraction within ± 0 75 DS with 36 older subjects differences in age were between 24 and 56 years (mean difference 34 78 years) A Wilcoxon matched pairs signed ranks test was used to analyse the differences found Once again axial length (p = 0 013) corneal diameter (p = 0 02) horizontal and vertical corneal radii (p = 0 002 p = 0 046) and anterior chamber depth (p = 0 001) were all significantly less in the older than in the younger subjects

Lens thickness was greater (p = 0 001) and corneal astigmatism was against the rule rather than with the rule (p = 0 001) in the older group of subjects

Applanation tension was significantly greater in the old than in the young (p = 0 033) though no actual correlation between higher applanation tension and old age was found (r = + 0 026)

Discussion

Our evidence for a reduction in axial length with increasing age is based on a transverse or cross sectional survey i e a single measurement of ocular dimensions in one normal eye of each of 72 persons of widely differing age A longitudinal or cohort study based on repeated measurements in a group of the same individuals over a number of years would probably give more reliable evidence of such a change in axial length However proof of an increase in lens thickness (Priestley Smith 1883) and a reduction in depth of anterior chamber (Raeder 1922) with increasing age were also found in transverse or cross sectional surveys

The subdivision of subjects into young and old groups matched for sex

(VII) Thickness of the crystalline lens } from an antero posterior axis trace of the eye obtained by A scan ultrasonography

(VIII) Length of the vitreous body } from an antero posterior axis trace of the eye obtained by A scan ultrasonography

(IX) Axial length of the eyeball – found from the addition of (V) (VII) and (VIII)

Results

CORRELATIONS OF DIMENSIONS WITH AGE

Axial length in older subjects was significantly less than in younger subjects ($N = 72$ $r_s = -0\ 316$ $0\ 005 < p < 0\ 010$ a Spearman Rank Correlation test was used (see Fig 1 and Table I) Corneal diameter was also significantly less in the older subjects ($N = 53$ $r_s = -0\ 325$ $0\ 005 < p < 0\ 010$) As might have been expected anterior chamber depth become less and lens thickness greater with increasing age ($N = 72$ $r_s = -0\ 627$ and $+0\ 839$ respectively $p < 0\ 001$ in each case) Corneal astigmatism changed from "with" to "against the rule" with increasing age i e vertical radius was greater than horizontal radius in old age ($N = 72$ $r_s = +0\ 465$ $p < 0\ 001$) However both horizontal and vertical corneal radii actually diminished with increasing age ($N = 72$ $r_s = -0\ 535$ and $-0\ 268$ $p < 0\ 001$ and $0\ 025 < p < 0\ 050$

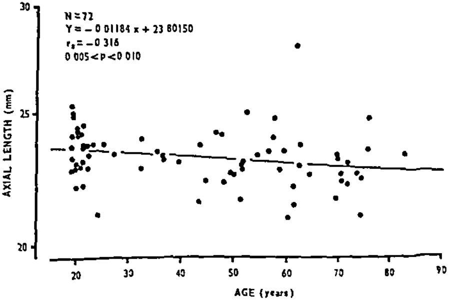


Fig 1

Scattergram of axial length of eyeball and age

shown by Grieten & Weekers (1962) and Storey & Phillips (1971) to be smaller in angle closure glaucoma than is normal A tendency for axial length and corneal diameter each to becom smaller with increasing age would tend to reduce anterior chamber depth and the effect of these changes would be added to those of increasing thickness of the lens and anterior chamber depth The multifactorial nature of the disease thus becomes more apparent

A reduction in corneal diameter with increasing age would also be a factor contributing to the small corneal height which is found in angle closure glaucoma (Storey & Phillips 1971) However in our normal sample corneal height was not age dependent ($p > 0.05$) although it might be in patients with angle closure glaucoma and perhaps to a lesser degree in their first degree relatives A correlation between corneal height and the age of onset of glaucoma in a group of patients with angle closure glaucoma would probably not be found because a threshold value has to be reached before angle closure occurs Relative lens position was also not age dependent in this study although Lowe (1970) found that it was in patients with angle closure glaucoma as well as in normals

IMPLICATIONS IN OPEN ANGLE GLAUCOMA

We found a tendency towards higher ocular tension in older subjects as has been found previously in population surveys (Armaly 1965 Graham & Hollows 1966 Bankes Perkins Tsolakis & Wright 1968 and others) This may be consistent with and explained by a tendency towards increased outflow resistance with age as has been found by Weekers Watillon & de Rudder (1956) Becker (1958) and Boles Carenini & Cambiaggi (1959) these findings were contradicted however by the findings of Grant (1951) de Roetth & Knighton (1957) and Spencer Helmick & Scheie (1955) Among patients with open angle glaucoma a small size of eyeball is associated with high ocular tension and a large eyeball with lower (though still increased) ocular tension (Leighton & Tomlinson 1972) A small size of eyeball is probably associated with a high outflow resistance A small eyeball usually has a relatively shallow anterior chamber with which a high outflow resistance is associated (François *et al* 1958 Barkhoff & Kaizik 1969)

An increase in applanation tension and outflow resistance with increasing age could be partly accounted for by a concomitant reduction in corneal size and hence a reduction in the circumference of angle available for the escape of aqueous from the eye It is interesting that although guttae homatropine provokes an elevation of intra ocular pressure and outflow resistance in pa

and refractive error (±0 75 DS) and differing in age by an average of 34 78 years allowed the use of a matched pairs statistical test This also revealed a significantly smaller axial length in the older subjects (p = 0 015) and confirmed the correlation found above (see Fig 1) between age and axial length Old subjects also had smaller corneal diameters than did young subjects (p = 0 02)

If as seems likely eyes in general become more hypermetropic with increasing age up to the age of 64 years (Slataper 1950 Duke Elder 1970) the difference we found in axial length between old and young groups would have been an underestimate because we matched each pair closely for refractive error i e the 1 00 D hypermetropic subject of 65 may well have been emmetropic at 25 years and therefore matching of a relatively "long old eye with a "shorter young one should have discriminated against the findings we obtained

Comparison of young and "old" groups agreed with the trends found in the correlations mentioned above between age and anterior chamber depth lens thickness corneal astigmatism and corneal radius (see Table II)

The presence in our sample of the expected tendencies for anterior chamber depth to be less lens thickness greater corneal astigmatism against rather than "with the rule and above all the horizontal corneal diameter to be smaller in the old than in the young subjects supports our evidence that the eyeball does become smaller with increasing age Lowe (1970) however found no correlation between axial length of eyeball and age in normal eyes

Changes in the physical properties of the eye with age may result in a change in velocity of transmission of ultrasound at different ages Lens thickness and vitreous length were measured by ultrasound and anterior chamber depth was added to these to calculate axial length On the one hand an increased density of the crystalline lens in old age could result in a more rapid passage of the ultrasound and an underestimate of lens thickness and hence also of axial length On the other hand liquefaction of the vitreous in old age could result in a reduction in density and a less rapid passage of ultrasound so that vitreous length and hence axial length would be overestimated Perhaps the effects of changes in properties of the lens and vitreous at different ages on the velocity of ultrasound would tend to cancel each other out

IMPLICATIONS IN ANGLE CLOSURE GLAUCOMA

Lowe (1970) and Storey & Phillips (1971) found a small eyeball in angle closure glaucoma compared to the normal Corneal diameter has also been

shown by Grieten & Weekers (1962) and Storey & Phillips (1971) to be smaller in angle closure glaucoma than is normal A tendency for axial length and corneal diameter each to become smaller with increasing age would tend to reduce anterior chamber depth and the effect of these changes would be added to those of increasing thickness of the lens and anterior chamber depth The multifactorial nature of the disease thus becomes more apparent

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An increase in applanation tension and outflow resistance with increasing age could be partly accounted for by a concomitant reduction in corneal size and hence a reduction in the circumference of angle available for the escape of aqueous from the eye It is interesting that although guttae homatropine provokes an elevation of intra ocular pressure and outflow resistance in pa

tients with open angle glaucoma no such effect is ususally found in normals (Christensen & Pearce 1963 Barany & Christensen 1967) This elevation in intra ocular pressure and outflow resistance after guttae homatropine is greater in eyes with small corneal diameter than in those with large corneal diameter (Leighton & Tomlinson 1971)

A reduction in the size of the whole corneo scleral envelope would lead to a reduction in the size of spaces between the collagen fibres in the trabecular meshwork as well as the scleral outlets concerned in uveo scleral bulk flow (Bill & Phillips 1971) and thus lead to an increased resistance to the outflow of aqueous and raised intra ocular pressure From the regression line on Fig 1 it can be seen that the axial length at 20 years is 23 56 mm and at 70 years 22 97 mm If the eyeball is assumed to be spherical (it is of course ellipsoidal) the corresponding surface areas for the corneo scleral envelope are 174 2 and 165 8 mm² This represents only a small change in surface area between the ages of 20 and 70 years although it is possible that this change can have a considerable effect on the size of aqueous outflow channels

Patients with open angle glaucoma may show a greater tendency towards reduction in size of eyeball with increasing age than do normals thus con tributing to raised intra ocular pressure as one facet of a multifactorial aetiology A reduction in size of both optic disc and cup and hence reduced *susceptibility to raised intra ocular pressure might in some cases result* thus perhaps explaining the good tolerance to raised intra ocular pressure observed in some eyes Relatives of patients with open angle glaucoma might also be expected to show some exaggeration in a tendency to reduction of eyeball size with age Armaly (1965) has shown that they fit into the group of individuals in population surveys whose intra ocular pressure increases with increasing age

Such a small though perhaps important reduction in the size of the eyeball with advancing age as we have found would not necessarily be associated with obvious alterations in the micro or ultra structure of the corneoscleral envelope and its constituent collagen fibres This may explain why no clear differences have yet been found in the microstructure of the trabecular meshwork between that found in patients with open angle glaucoma and eyes from normal persons of the same age (Rohen 1970) An exaggeration of a normal shortening in the corneo scleral envelope *perhaps in the especially important region* of the trabecular meshwork may be present in open angle glaucoma and such a change would be difficult to recognise by microscopy

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SPONTANEOUS ELECTRICAL ACTIVITY IN DENERVATED EXTRA OCULAR MUSCLES

BY

SVEND FAURSCHOU JENSEN

The occurrence of fibrillation potentials and their duration and amplitude were studied in denervated extra ocular muscles from both rabbits and humans Denervation was total in the rabbits and of various degrees in the humans Fibrillation potentials were recorded from the denervated rabbit muscles and from 23 of 58 human extra ocular muscles with neuro genic atrophy In the rabbit ocular muscles there was no difference in duration or amplitude between potentials of motor units and fibrillation potentials In the human ocular muscles the mean duration of 66 fibril lation potentials was 2 0 msec s d 0 4 msec, and the mean duration of the motor unit potentials was ? 8 msec s d 0 4 msec The mean amplitude of the human fibrillation potentials was 88 μV s d 52 μV and the mean amplitude of the motor unit potentials was 102 μV s d 58 μV In the human ocular muscles 95 % of the recorded fibrillation potentials were simple triphasic potentials In the rabbit ocular muscles the distribution of potentials by phase was approximately the same for normal and for de nervated muscles

Key words electromyography – fibrillation potentials – extra ocular muscles

Partially or totally denervated muscle shows spontaneous activity consisting of fibrillation potentials and positive sharp waves Since they originate from a single or a few muscle fibre(s) the fibrillation potentials have much *shorter*

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duration and lower amplitude than the motor unit potentials The time at which this activity first appears after the injury depends on the length of the axon distal to the nerve lesion (Luco & Eyzaguirre 1955) Buchthal & Rosenfalck (1966) recorded fibrillation potentials from the extensor digitorum communis muscle as early as five days after injury to the radial nerve

When the eye is in the primary position the extra ocular muscles show continuous activity Only during maximum contraction of the agonist is there little or no activity in the motor units of the antagonist In a partially denervated extra ocular muscle it is often difficult to identify fibrillation potentials since the potentials of the motor units are of short duration and low amplitude Thus some workers have not recognized fibrillation potentials in the extra ocular muscles (Kamouchi 1955) whereas others have reported them (Björk 1954 Huber & Lehner 1956 Breinin & Moldaver 1955 Breinin 1957 1962 Teasdall & Sears 1959 Gamstorp & Kupfer 1960 Skorpil et al 1963 Anastassopoulos et al 1964 Wojtowics 1969) Esslen & Papst (1961) suggested that fibrillation potentials were less common in the extra ocular than in skeletal muscles They described the fibrillation potentials as diphasic with a duration of 1–2 msec and an amplitude of 5–100 μV occurring in an irregular sequence at a frequency of 1–5 per sec

The aim of the study presented in this report was 1) to establish when fibrillation potentials occur after denervation of the extra ocular muscle of the rabbit 2) to determine what percentage of partially or totally denervated extra ocular muscles in man display fibrillation potentials and in how many sites of the muscle they are recorded and 3) to compare the duration and amplitude of fibrillation potentials and of motor unit potentials in the extra ocular muscles of rabbit and of man

Method

RABBIT MUSCLES

Two rabbits weighing 3 kg were used The denervation was performed under Nembutal® anaesthesia injected i p (40 mg kg) supplemented when necessary by injection into an ear vein The superior rectus muscle was denervated by resectioning a 2 mm portion of the oculomotor branch to the muscle after access had been obtained to the retrobulbar space by ronguring the upper orbital margin away and by cutting the attachment of the muscle to the eyeball After removal of the nerve the tendon of the muscle was re sutured to the eyeball The anterior tibial muscle was denervated by excising a 5 mm long segment

of the peroneal nerve 2 cm proximal to the entrance of the nerve into the muscle The postoperative course was uncomplicated After denervation recordings were taken both from the denervated and from the contralateral normal muscles The first recording under light anaesthesia was taken on the second day after denervation thereafter every other day for one week then once weekly and then every other week over a total period of 4½ to 5 months The rabbits were killed by anaesthesia and the normal and denervated superior rectus and anterior tibialis muscles were removed fixed in 4 % formalin and stained by the method of Van Gieson Hansen (prepared by the Ophthalmic Pathology Laboratory University of Copenhagen) The diameter of 200 muscle fibres in the normal and in the denervated muscles was measured in sections through the thickest part of the muscle belly

HUMAN MUSCLES

Recordings were taken from 58 muscles (54 patients) with lesions of the oculo motor or abducens nerve 10 days to 64 years after the onset of paresis Judging from the electromyographic findings 11 of the 58 muscles were totally denervated (i e no activity of motor units) and 47 were partially denervated (activity of motor units more or less) Clinically the paresis was slight in 9 muscles and severe or total in 49 muscles The cause of the paresis of the extra ocular muscles was injury to the orbit or skull in 13 cases intracranial tumour in 6 cases vascular lesions in 19 cases sclerosis disseminata in 3 cases congenital paresis in 4 cases and unknown in 9 cases

ELECTRODES

For recording from the denervated and the normal contralateral ocular muscles a concentric electrode with a leading off area of 0 015 m and an outer diameter of 0 3 mm (Faurschou Jensen 1971) was used To record from the denervated and the contralateral normal anterior tibial muscles of the rabbit a concentric electrode was used with a 5 times greater leading off area (Disa 13 K 03) The electromyograph was a Disa type 13 A 69 with 3 channels The input impedance of the amplifier was 100 MΩ parallel with 60 pF the noise level was 2 μV r m s The lower limiting frequency was 3 Hz the upper 10⁴ Hz (3 db down)

The duration of the fibrillation potentials and of the motor unit potentials was measured from the first deflection from the baseline to the return to the baseline (total duration) The amplitude was measured peak to peak

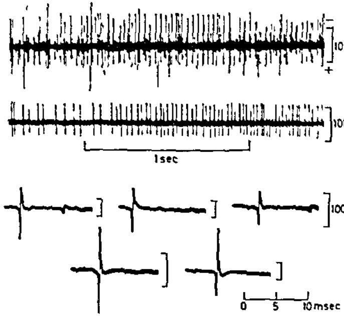


Fig 1

Fibrillation potentials in the superior rectus muscle of the rabbit five days after denervation Top Different fibrillation potentials Middle Single fibrillation potential with irregular frequency Lowest Samples of fibrillation potentials recorded at faster sweep speed

Results

MUSCLES OF RABBITS

In both rabbits fibrillation potentials appeared in the ocular superior rectus muscles from the third day after denervation (Fig 1) Profuse spontaneous activity was present in each of eight different positions of the electrode in the muscle examined In the denervated anterior tibial muscles fibrillation potentials were also recorded from the third day they were however less frequent and occurred only in one of ten sites examined Fibrillation potentials in all ten sites examined were not recorded until 8–9 days after denervation Positive sharp waves occurred in addition to fibrillation potentials both in the ocular superior rectus and in the anterior tibial muscles During 4½ and 5 months of observation the spontaneous activity gradually decreased in incidence and denervation potentials were still recorded in more sites of the ocular superior rectus than of the anterior tibial muscle Pseudomyotonic bursts were common both in the superior rectus and the anterior tibial muscles

Table I

Duration and amplitude of fibrillation potentials and motor unit potentials in the superior rectus and anterior tibial muscles of the rabbit (positive sharp waves not included)

	Duration msec	s d msec	s e msec	Amplitude μV	s d μV	s e μV	Maximal amplitude μV	N
Denervated rectus muscle superior fibrillation potentials	2.7	1.0	0.1	115	93	8.7		114
Normal superior rectus muscle motor unit potentials	2.7	0.7	0.07	91	60	5.9	300	102
Denervated anterior tibial muscle fibrillation potentials	2.7	0.6	0.06	115	66	6.5		103
Normal anterior tibial muscle motor unit potentials	6.1	2.4	0.24	167	204	20.2	800	102

In the ocular rectus muscles the mean duration and amplitude were the same for motor unit potentials and fibrillation potentials In the anterior tibial muscles the mean duration of the fibrillation potentials was 55% shorter and their amplitude 30% lower than that of motor unit potentials (Table I) The different shapes (number of phases) of 100 successively recorded fibrillation potentials and motor unit potentials from the superior rectus and anterior tibial muscles are shown in Table II This Table also gives the incidence of positive sharp waves which was three times greater in the denervated anterior tibial than in the denervated superior rectus muscles Also from the normal superior

Table II

Occurrence of different shapes of fibrillation potentials and of motor unit potentials in the superior rectus and anterior tibial muscles of the rabbit Irregular potentials are defined as potentials with irregularities in the shape of the positive or negative deflections from the baseline

	Denervated superior rectus muscle		Normal superior rectus muscle		Denervated anterior tibial muscle		Normal anterior tibial muscle	
Shape of potentials	fibrillation potentials		motor unit potentials		fibrillation potentials		motor unit potentials	
		%		%		%		%
Positive sharp waves	6	5.5	3	3.0	19	17.3	2	2.0
Diphasic	19	17.3	21	20.8	24	21.8	36	35.6
Triphasic	70	63.7	66	65.3	63	57.3	54	53.5
Tetraphasic	5	4.6	4	4.0	2	1.8	6	5.9
Polyphasic			7	7.0			3	3.0
Complex	10	9.0			2	1.8		
(Irregular potentials)	21	19.9	16	15.7	19	17.3	25	24.5
Total number	110		101		110		101	

rectus and anterior tibial muscles a few positive sharp waves were recorded The distribution of potentials with two to four phases was approximately the same in normal and in denervated muscles Polyphasic potentials (potentials with more than four phases) were recorded from the normal superior rectus and anterior tibial muscles Potentials with more than four phases were also recorded from the denervated muscles but these potentials – complex potentials – originate from different fibrillating muscle fibres contracting with a constant time interval The discharge frequency of the fibrillation potentials in the denervated muscles was measured when the individual potentials could be distinguished for at least 5–4 sec In the superior rectus as well as in the anterior tibial muscles the discharge frequencies ranged from 1–40 per sec

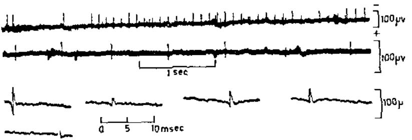


Fig 9
Fibrillation potentials in the human medial rectus muscle

The average diameters of the muscle fibres in the denervated superior rectus and anterior tibial muscles were respectively 30 and 38 % less than the mean diameter of the muscle fibres in the contralateral normal muscles The mean diameter of normal fibres in the anterior tibial muscle was 35 1 μ s d 8 0 μ N 400 in denervated anterior tibial muscle it was 21 4 μ s d 6 1 μ N 400 The mean diameter of normal fibres in superior rectus muscles was 25 8 μ s d 5 6 μ N 400 in denervated muscles it was 18 3 μ s d 4 6 μ N 400

HUMAN OCULAR MUSCLES

Fibrillation potentials were recorded in 23 of 58 muscles with neurogenic pa resis (Fig 2) They were found in totally as well as partially denervated mus cles They were also present in four muscles in which signs of paresis were mild and in which there was no electromyographic loss of motor units The remaining 19 muscles were clinically severely to totally paretic From 1 to 12 different fibrillation potentials could be recorded in each muscle and from 1-3 different fibrillation potentials per site Of the recorded fibrillation po tentials 93 % were regular triphasic potentials a few were di and tetraphasic and only two potentials were irregular No fibrillation potentials with more than four phases were recorded

The duration of the fibrillation potentials ranged from 1 0 to 3 0 msec with a mean duration of 2 0 msec s d 0 4 msec (61 potentials) The mean amplitude was 88 μV s d 52 μV (5 to 310 μV) The discharge frequency was slow from 1 2 per sec maximum 20 per sec

A single positive sharp wave was recorded from only 4 of 23 muscles Pseudo myotonic bursts were found in 3 of the muscles examined

Discussion

The study presented here demonstrates the presence of fibrillation potentials in the denervated superior rectus and anterior tibial muscles in rabbit and in human extra ocular muscles with neurogenic atrophy

In the rabbit ocular muscles the fibrillation potentials were of the same duration and amplitude as the motor unit potentials In the anterior tibial muscle the mean duration of the fibrillation potentials was about 50 % of normal and the mean amplitude about 65 % of the amplitude of normal motor unit potentials Sakatani & Jampel (1964) recording from denervated cat and monkey ocular muscles also found no difference in duration and amplitude between fibrillation potentials and motor unit potentials Considering that the diameter of the muscle fibres in the denervated rabbit ocular muscles was 30 % smaller than in the normal control muscles at the end of 5 months a reduction in the potential duration and amplitude might have been expected (Håkansson 1957 Rosenfalck 1969) The difference in diameter of the muscle fibres was 38 % for the anterior tibial muscles in which the mean duration of fibrillation potentials was just below 50 % of the mean duration of normal motor unit potentials

Since 9 % of potentials in denervated superior rectus and 2 % of potentials in denervated anterior tibial muscles were complex these potentials were derived from more than one muscle fibre The positive sharp waves in normal muscles were presumably due to injury of muscle fibres to the electrodes (Table II)

The discharge frequencies of fibrillation potentials were the same in the superior rectus and in anterior tibial muscles and were the same as the frequencies found by Buchthal & Rosenfalck (1966) in skeletal muscles and by Sakatani & Jampel (1964) in denervated cat and monkey extra ocular muscles

Fibrillation potentials were found in 38 % of human extra ocular muscles with neurogenic atrophy In skeletal muscles Buchthal & Pinelli (1953) found fibrillation potentials in about 70 % of muscles with neurogenic atrophy The proportion would presumably have been still higher if the muscles had been warmed (Hnik & Skorpil 1959) A single fibrillation potential was recorded in 8 of the 23 muscles with fibrillation potentials It is difficult to explain why fewer fibrillation potentials occur in ocular than in skeletal muscles with neurogenic atrophy One explanation might be that some muscle fibres in the individual motor units are innervated by several nerves some of which remain intact Such intact nerve fibres might prevent fibrillation but not be sufficient to produce voluntary contraction It may be that some of the muscle fibres in

the extra ocular muscles do not fibrillate or human ocular and skeletal muscles may not be comparable in this respect

The mean amplitude of fibrillation potentials was within the range of normal action potentials (102 μV s d 58 μV N 408) whereas the mean duration of ?0 msec was 25% shorter than the mean duration for normal action potentials (?8 msec s d 0 4 msec N 408) In the brachial biceps muscle Buchthal & Rosenfalck (1966) found that the mean duration of fibrillation potentials was reduced to about 25% of the mean duration of motor unit potentials whereas the mean amplitude was of the same magnitude for fibrilla ion and motor unit po entials From normal ocular muscles too action potentials of low amplitude and short duration may be recorded Out of 408 normal action potentials 54% had an amplitude between 30 and 90 μV and 7% had a duration between 1 6 and ? ? msec Neither endplate activity nor fibrillation potentials have been recorded in normal extra ocular muscles (Faurschou Jensen 19?1)

It may be difficult to distinguish fibrillation potentials from motor unit potentials in the extra ocular muscles e pecially if there is ample voluntary activity The fibrillation potentials in the extra ocular muscles may be identified by the short duration and by the absence of an increase in discharge frequency when the muscle is activated

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ON THE OSCILLATORY POTENTIALS OF THE HUMAN ELECTRORETINOGRAM IN LIGHT AND DARK ADAPTATION

II Effect of adaptation to background light and subsequent recovery in the dark A Fourier analysis

BY

P ALGVERE and L WACHTMEISTER

The effect of adaptation to backgrounds of different light intensities and subsequent recovery in the dark of the oscillatory potentials and a and b waves of human ERG was studied The total energy and dominant frequency of oscillatory potentials were calculated by a combined impulse response and Fourier analysis
When recorded in response to strong flashes of light (colour temperature 6500 K) given at 3 minute intervals in dark adaptation the oscillatory potentials showed a small amplitude and a high frequency (around 145 Hz) On adaptation to a background of about 10 photopic candelas/m which corresponds to the cone threshold the amplitude of the oscillatory potentials was enhanced and the dominant frequency changed to 90–100 Hz At a background of about 1 candela/m where the sensitivity of the photopic b wave becomes higher than that of the scotopic b wave there was a decline in the total energy of the oscillatory potentials At rod saturation no change in energy nor in frequency of the oscillatory potentials was observed During adaptation to darkness the dominant frequency of the oscillatory potentials changed from 90–100 Hz to around 145 Hz as the energy of the oscillatory potentials decreased
When adapted to a background the intensity of which was above the cone threshold the oscillatory potentials were always present When the b wave was suppressed by a background light the total energy of the oscillatory

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potentials decreased The oscillatory potentials are related to photopic retinal function but seem to be influenced also by the scotopic system as well

Key words electroretinography – oscillatory potentials – light and dark adaptation – Fourier analysis – background light intensity – recovery in the dark

Ever since the observations of Kühne & Steiner (1880) the electric retinal response has been known to decrease in amplitude when the retina is adapted to backgrounds of successively increasing light intensity For example the scotopic b wave of the electroretinogram (ERG) is especially sensitive and is depressed even at very weak intensities In the rod dominated rat retina the decrease in the logarithm of sensitivity of the b wave seems to be linearly related to the increase in the logarithm of background luminance (Dowling 1967 Weinstein Hobson & Dowling 1967)

Since the a wave of the ERG is a photoreceptor potential and the b wave originates from cells in the inner layers of the retina it is not surprising that their behaviour on adaptation to light is different By means of intraretinal microelectrodes Brown & Watanabe (1965) recorded a local b wave from the retina of the cynomolgus monkey In response to repetitive light stimuli the local b wave was considerably reduced in amplitude while the reduction of the a wave was insignificant After blocking the retinal circulation the a wave or P III in Granit s (1933) terminology could be isolated and this response also showed no decrease on adaptation to the weak light stimuli given

The a wave of the rat s ERG recorded with a corneal electrode shows little if any adaptation to low background intensities but at high background illumination it quickly and sharply saturates (Cone 1964 Cone & Ebrey 1965 Dowling 1967) But from cone dominated retinas (such as the pigeon s eye) as well as from the human eye a photopic a wave can be elicited even if adapted to comparatively strong light

In his pioneering work on the electric response of the frog s eye Holmgren (1865) observed that the response gained in amplitude during dark adaptation Now it is generally accepted that the recovery of the retinal response in the dark is rapid when the adapting light is weak and nonbleaching but slow after exposure to light that bleaches a significant fraction of photopigments (Elenius & Ahlas 1961 Dowling 1963 Dowling & Ripps 1971)

The a wave and the b wave have different rates of adaptation to darkness In the cat s eye the slow recovery in the dark of the b wave could be compared to rapid adaptation to darkness of the isolated P III (Maffei & Poppele 1966)

In the human eye also the a wave gains in amplitude much faster than the b wave (Elenius 1967)

The qualitative similarities and quantitative differences in the adaptation of the b wave and P III have been further analysed in the absence of photopigment regeneration in the isolated frog retina (Frank 1971)

Contrary to the a and b waves the behaviour of the oscillatory potentials of the human ERG has not been elucidated on adaptation to backgrounds of various intensities and during the subsequent recovery in darkness The aim of the present work was to study the amplitude latency and frequency of the oscillatory potentials by means of a mathematical evaluation use being made of a combined impulse response and Fourier analysis (Algvere & Westbeck 19?) This method gives more accurate estimates of the amplitude and frequency of the oscillatory potentials than has been obtained by previous measurements

Apparatus and Methods

Apparatus

Most of the equipment for recording the ERG was the same as previously described (Algvere Wachtmeister & Westbeck 1972)

The stimulus light source was an electronic flash lamp (Karpe & Algvere 19?) The colour temperature of the light corresponded to about 6500°K and the maximum luminance obtained on the lamp screen was about 5×10^4 photopic candelas/m The luminous flux attained a maximum in less than 2 msec and 50% of its peak intensity was maintained for about 2 5 msec (0 9 msec to 3 4 msec from the onset of light stimulus)

To enable adaptation to an illuminated background a tungsten filament lamp was used (Philips 6162 C/051 220V/500W) The filament lamp was put in a film projector its light beam diverged by a negative lens and projected on the viewing screen The colour temperature of the light was about 3150 K The maximum luminance of the background was measured with a Hagner Universal Photometer S1 to be about $1\ 5 \times 10^3$ photopic candelas/m corresponding to about $4\ 1 \times 10$ scotopic candelas m² when related to the CIE (Commission Internationale de l Eclairage 1951) scotopic luminosity curve The viewing screen subtended a visual angle of about 110 at the subject s eye The intensity of the stimulus and of the background light could be independently reduced by neutral density filters in a logarithmic scale

A corneal contact lens electrode with a built in reference electrode (Lawwill & Burian 1966) was used The ground electrode was placed on the ear lobe A double beam oscilloscope (Solartron CX 1442-3 or Hewlett & Packard 132A)

presented the timing on one cathode ray sweep and the ERG on the oth
When recording with the Hewlett & Packard oscilloscope rapid ERG respons
(oscillatory potentials) could be displayed in a high speed on one cathode r
sweep simultaneously with slow responses (a- and b waves) in a slow time sca
on the other

When recording slower components (a and b waves) the frequency respon
was unfiltered and flat for about 15–11 000 Hz and flat for about 80–5000 H
when the oscillatory potentials were recorded No active filter was used

The display on the oscilloscope screen was photographed in 1 1 scale by
Polaroid Land camera or 1 0 85 scale by a Hewlett & Packard oscilloscop
camera (198 A)

Methods of measurement

The methods of measurement of amplitudes and peak latencies were previousl
described as well as the mathematical evaluation of the frequency of the ER
by means of a combined impulse response and Fourier analysis and the fina
calculation of the energy of the oscillatory potentials (Algvere & Westbec
1972 Algvere Wachtmeister & Westbeck 1972)

Procedures

Investigations were made on one eye of four young and healthy persons thre
women and one man The *visual acuity visual fields* adaptometric visual sen
sitivity and colour sense were normal The ERG pictures shown were all re
corded from the left eye of the same subject and evaluated by calliper square
and magnifier measurements of amplitudes and implicit times as well as by a
Fourier analysis

Surface anesthesia of the eye was induced by Novesin® (Wander) Maximal
mydriasis was established by Mydriacyl® (Alcon lab) The diameter of the
pupil was expanded to more than 6 mm The fellow eye was *occluded*

The following two procedures were performed

1 The ERG was recorded after at least 30 minutes of dark adaptation After
that a background illumination was turned on for a period of 5 minutes Finally
the background light was switched off and the recovery in the dark was studied
The light stimulus was kept at maximal intensity available (about 1 5 × 10⁴
photopic candelas/m) Stimulus flashes were given at constant intervals of 30
seconds These flashes caused a comparatively strong light adaptation of the
eye which persisted to the point of time when the next flash was delivered (30

seconds later) The procedure was repeated and the subject adapted to back grounds of different intensities varied over a range of 5 log units

* In another series of experiments very similar to the procedure described above light stimuli were given at long intervals *i e* 3 minutes The light adap tation caused by these flashes was very weak at the point of time (3 minutes later) when the next flash struck the eye The ERG was recorded after at least 30 minutes of dark adaptation After that the eye was adapted to backgrounds of various intensities (range 5 log units) for 6 minutes and the recovery in the dark after each intensity of background was recorded

Results

I STRONG LIGHT ADAPTATION CAUSED BY STIMULUS FLASHES

The effect of adaptation to a background illumination was studied on the a and b wave and oscillatory potentials of the ERG The electric retinal response was recorded (i) in dark adaptation (ii) during 5 minutes exposure to a back ground light and finally (iii) the recovery in the dark was studied The background illumination was varied over a range of 5 log units The light stimulus was of constant intensity and was delivered every 30 seconds which caused a strong light adaptation of the retina to the flashes

The oscillatory potentials

The appearance and the amplitude of the individual peaks of the oscillatory potentials varied with the intensity of the background light (Fig 1) During adaptation to a weak background illumination (log I_B = −5) the oscillatory potentials had the same appearance (amplitude and number of peaks) as in dark adaptation At a background intensity of log I_B = −4 the 4th oscillatory peak of the oscillatory potentials was not distinguishable and the 3rd peak had also decreased in amplitude When a stronger background was used (log I_B = −3) only the first 2 peaks of the oscillatory potentials could be seen and the amplitude of those further decreased on adaptation to brighter backgrounds (log I_B = −2 to 0) These observations are consistent with the findings of Rendahl (1958) Nagata (1962) and others

The summed amplitude of the oscillatory potentials was measured On adaptation to a background light of weak intensity (log I_B = 5) the summed amplitude of the oscillatory potentials was found to remain the same as that

presented the timing on one cathode ray sweep and the ERG on the other When recording with the Hewlett & Packard oscilloscope rapid ERG responses (oscillatory potentials) could be displayed in a high speed on one cathode ray sweep simultaneously with slow responses (a and b waves) in a slow time scale on the other

When recording slower components (a and b waves) the frequency response was unfiltered and flat for about 15–11 000 Hz and flat for about 80–5000 Hz when the oscillatory potentials were recorded No active filter was used

The display on the oscilloscope screen was photographed in 1 1 scale by a Polaroid Land camera or 1 0 85 scale by a Hewlett & Packard oscilloscope camera (198 A)

Methods of measurement

The methods of measurement of amplitudes and peak latencies were previously described as well as the mathematical evaluation of the frequency of the ERG by means of a combined impulse response and Fourier analysis and the final calculation of the energy of the oscillatory potentials (Algvere & Westbeck 1972 Algvere Wachtmeister & Westbeck 1972)

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Results

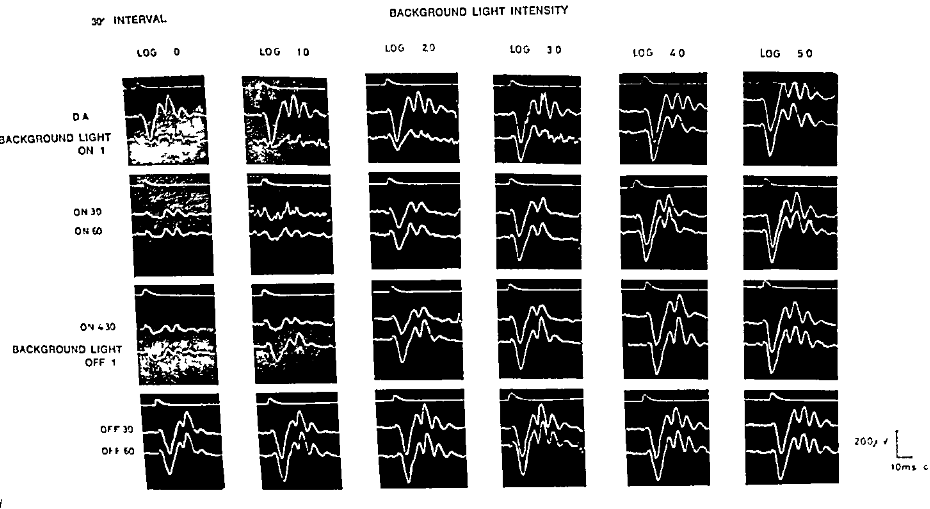
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The summed amplitude of the oscillatory potentials was measured On adaptation to a background light of weak intensity (log $I_B = -5$) the summed amplitude of the oscillatory potentials was found to remain the same as that


30' INTERVAL
BACKGROUND LIGHT INTENSITY
LOG 0
LOG 1.0
LOG 2.0
LOG 3.0
LOG 4.0
LOG 5.0
DA
BACKGROUND LIGHT ON 1
ON 30
ON 60
ON 430
BACKGROUND LIGHT OFF 1
OFF 30
OFF 60
200μV
10ms

recorded in dark adaptation (Fig 2) The summed amplitude decreased to about 40% of its value in dark adaptation when the eye was adapted to a background intensity of log $I_B = -3$ and it was reduced to less than 30% on adaptation to the brightest background (log 0)

To obtain more accurate estimates of the oscillatory activity the energy of oscillatory potentials was calculated The energy did not decrease in weak background illumination up to log $I_B = -4$ (Fig 3) On adaptation to more intense backgrounds (log -3 or stronger) there was a remarkable decrease of the energy of the oscillatory potentials to less than 20% of its value in dark adaptation In maximal background light (log $I_B = 0$) the energy of the oscillatory potentials attained only about 10% of that obtained in dark adaptation

The dominant frequency of the oscillatory potentials varied between 115–129 Hz but did not show any systematic changes as the background light intensity was increased in steps from log $I_B = -5$ to log $I_B = 0$ (Fig 4) The peak latencies of the first two oscillatory peaks (0_1 0_2) remained constant (Fig 5) The implicit times for the last two oscillatory peaks (0_3 0_4) seemed to increase but were not distinguishable on adaptation to stronger backgrounds (log $I_B = -3$ to 0)

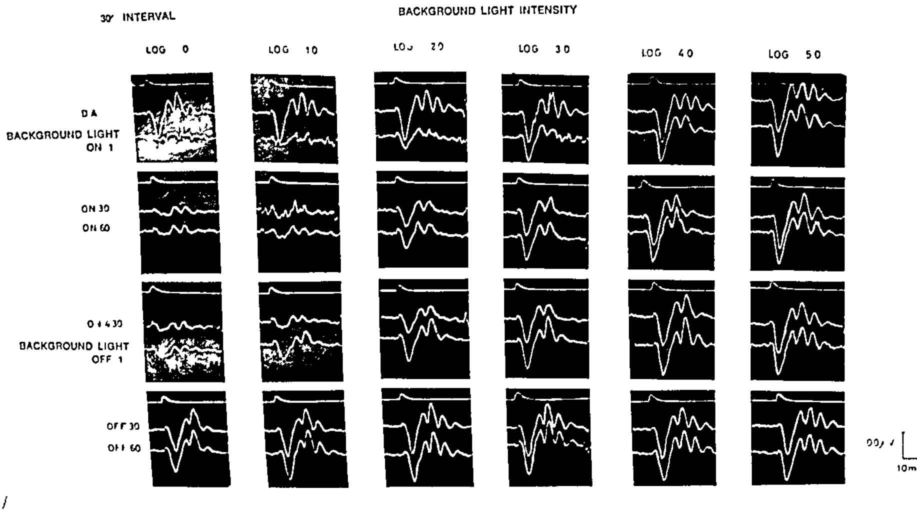
Recovery in the dark

After adaptation to background intensities of log $I_B = -2$ or weaker the recovery in the dark of all 4 oscillatory peaks was completed within 1 minute (Fig 1) At this point of time after adaptation to the strongest background (log $I_B = 0$) however the 4th oscillatory peak was not visible and even the amplitude of the 3rd peak was smaller than in dark adaptation The recovery in the dark of oscillatory potentials showed a characteristic pattern the first two peaks developed rapidly the last two or three peaks gained slowly in amplitude These observations are consistent with the findings of other authors (Samson Dollfus & Lods 1963)

Generally the recovery in the dark of the oscillatory potentials was rapid after adaptation to a background intensity of log $I_B = -2$ or weaker Within 1

Fig 1

Oscillatory potentials on adaptation to background light of different intensities Strong light adaptation caused by stimulus flashes ERG s were recorded in response to stimulus flashes given every 30 seconds in dark adaptation (D A) during 5 minutes of adaptation to a background light and during subsequent recovery in the dark The ERG s illustrated were recorded in dark adaptation (D A) and within 1 second at 30 seconds and 4 minutes and 30 seconds after the background light was switched on and within 1 second at 30 seconds and 60 seconds after cessation of background.



30' INTERVAL
BACKGROUND LIGHT INTENSITY
LOG 0
LOG 10
LOG 20
LOG 30
LOG 40
LOG 50
DA
BACKGROUND LIGHT
ON 1
ON 30
ON 60
ON 30
BACKGROUND LIGHT
OFF 1
OFF 30
OFF 60
10m

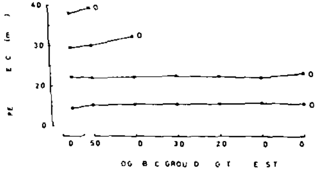


Fig 4

Dominant frequency of oscillatory potentials in relation to background light of different inten ties Stron light adaptation caused by stimulus flashes
The frequency is calculated from the ERG s shown in Fig 1 when adapted to back grounds of different intensities for 4 minutes and 30 seconds

minute in the dark the summed amplitude of the oscillatory potentials had reached almost the same value as in dark adaptation (Fig 2) When adapted to the strongest background used (log $I_B = 0$) the recovery was delayed and the summed amplitude of the oscillatory potentials was not as large as in dark adaptation when recorded after 5 minutes 30 seconds in darkness

A calculation of the energy of the oscillatory potentials also demonstrated that



F g 5

Peak laten ies of individual oscillatory potentials (O_1 O O_3 O_4) on adaptation to back gr und l ght of d fferent intensities Strong light adaptation caused by stimulus flashes
The values are measur d from ERG s shown in Fig 1 at 4 m nutes and 30 seconds adaptation to background of different intensit es The average error of rej etitive cal l pe square eading was less than 0 5 msec

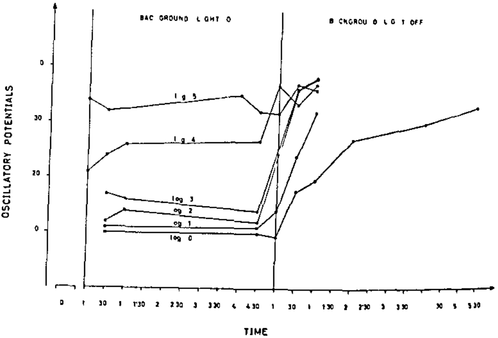


Fig 2

Summed amplitude of individual oscillatory peaks on adaptation to background light of different intensities Strong light adaptation caused by stimulus flashes Oscillatory potentials are measured in arbitrary units (mm) from EPG s recorded with the procedure described in Fig 1 and plotted against time scale on x axis The calibration used was 0 1 mV–10 msec/cm

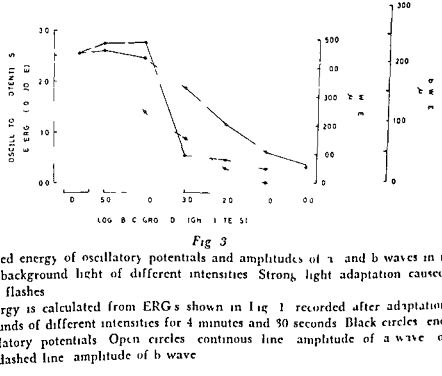


Fig 3

Calculated energy of oscillatory potentials and amplitudes of a and b waves in relation to background light of different intensities Strong light adaptation caused by stimulus flashes

The energy is calculated from ERG s shown in Fig 1 recorded after adaptation to backgrounds of different intensities for 4 minutes and 30 seconds Black circles energy of oscillatory potentials Open circles continous line amplitude of a wave open circles dashed line amplitude of b wave

recovery of the 3rd and 4th oscillatory peaks was not completed until 5 minutes in the dark

Frequency

After adaptation to the strongest background (log $I_P = 0$) the dominant frequency of the oscillatory potentials decreased reaching a minimal value (about 100 Hz) after 1 minute in the dark (Fig 7) On further adaptation to darkness the frequency showed a tendency to increase Five minutes after the background light was switched off the dominant frequency had reached almost the same value as that in dark adaptation (about 120 Hz) This change of frequency can also be seen as differences in implicit times on the isolated oscillations shown in Fig 9

However the implicit times of the individual oscillatory peaks when measured from the total ERG did not show any significant changes during recovery in the dark (Fig 8)

The a wave

As shown in Fig 3 the amplitude of the a wave was not significantly reduced on adaptation to backgrounds of weak intensity (log $I_B = -5$ and -4) When adapted to stronger backgrounds however each increment in log background intensity produced a fairly uniform decrease of the a wave amplitude until a background luminance of log $I_B = -1$ was reached Further augmenta

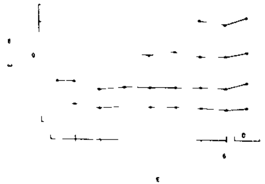


Fig 8

Peak latencies of individual oscillatory potentials (O_1 O_2 O_3 O_4) during recovery in the dark after adaptation to a background of maximal intensity (log $I_B = 0$) Strong light adaptation caused by stimulus flashes The procedure for recording the ERG was the same as described in Fig 6 There was no significant change in peak latencies during adaptation to darkness The same error of measurements as in Fig 5

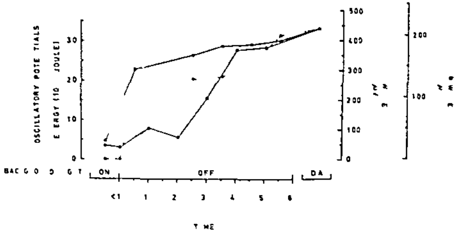


Fig 6

Calculated energy of oscillatory potentials and amplitudes of a and b waves durin recovery in the dark after adaptation to a background of maximal intensity (log $I_B = 0$) Strong light adaptation caused by stimulus flashes ERGs were recorded every 30 seconds alternatively with a rapid cathode ray sweep speed (oscillatory potentials) or with slow speed (a and b waves) Black circles energy of oscillatory potentials open circles continous line amplitude of a wave open circles dashed line amplitude of b wave

their recovery was delayed during the first 2 or 3 minutes in the dark contrary to the amplitudes of the a and b waves After that point of time larger oscil latory potentials almost as in dark adaptation were recorded (Fig 6) The

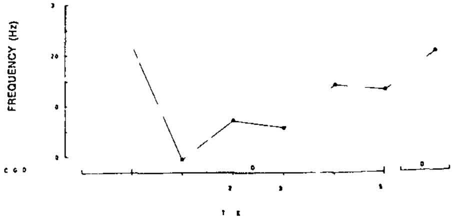


Fig 7

Dominant frequency of oscillatory potentials during recovery in the dark after adapta tion to a background of maximal intensity (log $I_B = 0$) Strong light adaptation caused by stimulus flashes The procedure was the same as described in Fig 6 The dominant frequency varied between 99 and 122 Hz

successively decreased but in uneven steps initially by larger steps and on adaptation to stronger backgrounds by smaller steps No b wave was recordable above the iso electric line against the strongest background intensity ($\log I_B = 0$) but a small a wave was present

The recovery curve in the dark for the b wave showed a break (alpha point) at 4–5 minutes after cessation of the strongest background light (Fig 6)

It appears from these experiments that the a wave and the oscillatory potentials were not significantly reduced on adaptation to backgrounds of low intensities ($\log I_B = -4$ or weaker) as depicted in Fig 3 When the amplitude of the a wave was plotted against log background intensity the curve was S shaped This was very prominent also for the oscillatory potentials curve The b wave on the other hand was considerably reduced at low background intensities and was suppressed from above the iso electric line when recorded at the strongest backgrounds ($\log I_B = -1$ and 0) This difference recorded in the present study between the a wave and the b wave is in accordance with the results reported by Dowling (1967) on rat s ERG and Winkler (1972) on rabbit s ERG

After adaptation to backgrounds of various intensities the recovery in the dark of the oscillatory potentials was different from that of the a and b waves As shown in Fig 6 the a wave had a monophasic recovery curve in the dark even if adapted to the strongest background used in this experiment The recovery curve of the b wave probably had a kink after 4–5 minutes in the dark The recovery of the oscillatory potentials was delayed during the first 2–3 minutes in the dark It must be pointed out that this recovery is affected by the flashes given every 30 seconds which seems to influence especially the regeneration of oscillatory potentials (*cf* Fig 15 where flashes were delivered at 3 minute intervals)

II WEAK LIGHT ADAPTATION CAUSED BY STIMULUS FLASHES

The ERG was recorded (i) in dark adaptation (ii) during 6 minutes of exposure to a background light and (iii) during the recovery in the dark

The background light was varied over a range of 5 log units of intensity The light stimulus was of constant intensity and was delivered with intervals of 3 minutes This caused a weak retinal light adaptation at the point of time when the next flash was given (3 minutes later) The results were evaluated and compared to those obtained when flashes were given every 30 seconds

The oscillatory potentials

When stimulus flashes were given at intervals of 3 minutes in dark adaptation

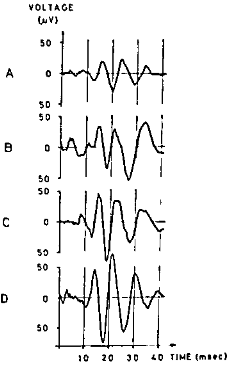


Fig 9

Oscillatory potentials isolated from ERG s recorded during recovery in the dark as in Fig 6 The ERG was recorded in maximal background illumination ($\log I_B = 0$) shown in Fig A and after 1 minute (B) 3 minutes (C) and 5 minutes (D) respectively in the dark

tion of background intensity ($\log I_B = 0$) was accompanied only by a slight reduction of the a wave The a wave finally decreased to about 75 μV corresponding to less than 20 % of its value in dark adaptation (about 440 μV)

The recovery of the a wave in the dark after adaptation to a background intensity of $\log I_B = -1$ or weaker was completed within 1 minute Within 1 second after cessation of background light a double peaked a wave was recorded After adaptation to the strongest background used ($\log I_B = 0$) the a wave reached its maximal value after 3 minutes 30 seconds in the dark (Fig 6) No kink (alpha point) on the recovery curve was observed in this experiment (cf Brunette 1971)

The b wave

The b wave was very sensitive to light adaptation and was considerably depressed even by weak background illumination Its amplitude decreased about 10 % on adaptation to a weak background light ($\log I_B = -5$) (Fig 3) For each increment of 1 log unit of background intensity the b wave amplitude

the shape and size of the ERG was different from the response recorded every 30 seconds The first positive peak of the ERG was ample and dominating and was followed by a marked negative trough which in turn was succeeded by in distinct oscillatory potentials of low amplitude

On adaptation to backgrounds of weak intensities (log $I_B = -5$ and -4) the amplitude of the oscillatory potentials increased distinctly as compared to the response obtained in dark adaptation (Fig 10) Further increments in back ground luminance however reduced the oscillatory potentials considerably leaving only the first 2 or 3 peaks distinguishable on the ERG

When recorded in weak background illumination (log $I_B = -5$ and -4) the summed amplitude of the oscillatory potentials also was measured to be larger than in dark adaptation (Fig 11) but when the intensity of background light further augmented there was a decrease of the summed amplitude of the oscillatory potentials On adaptation to maximal background intensity (log $I_B = 0$) the summed amplitude of the oscillatory potentials was measured to be about half of the value obtained in dark adaptation prior to light adaptation to the background

To obtain more accurate results the energy of the oscillatory potentials was calculated It likewise increased on adaptation to a weak background (log $I_B = -5$) and attained a maximum at a background intensity of log $I_B = -4$ (Fig 12) On adaptation to a moderate background intensity (log $I_B = -3$) the oscillatory potentials energy declined and remained low when recorded against stronger backgrounds (log $I_B = -2$ or stronger)

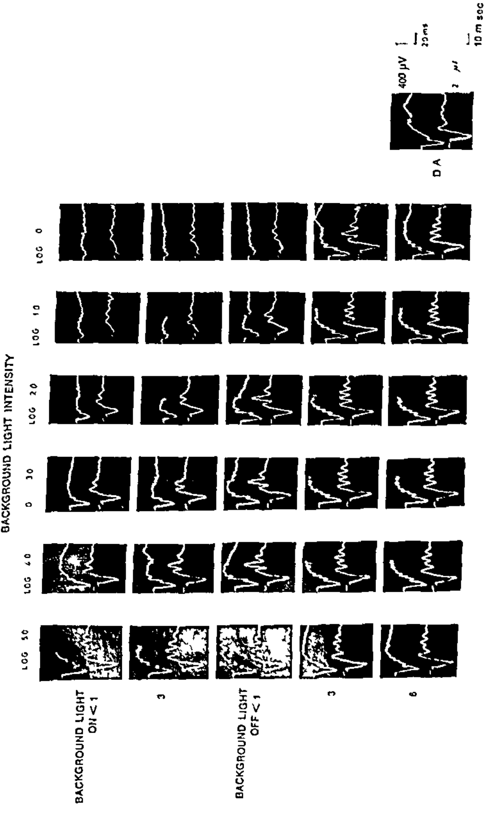
The *dominant frequency* of the *very small oscillatory potentials recorded in* dark adaptation was around 145 Hz (Fig 13) On adaptation to a background of weak intensity (log $I_B = -5$) the frequency immediately decreased to about 100 Hz There was no further change in frequency on adaptation to stronger background intensities (log $I_B = -4$ to 0) and the dominant frequency remained between 93–100 Hz

Fig 14 shows the implicit times for the individual oscillatory peaks on adap tation to successive increments in background luminance The transition from dark adaptation to a weak background illumination (log $I_B = -5$) seems to be associated with certain changes in implicit times Stronger backgrounds induce no systemic change in peak latencies It must be pointed out that little informa

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Fig 10

Oscillatory potentials and a and b waves recorded in dark adaptation (D.A) and on adaptat on to backgrounds of different ntensities Weak light adaptation caused by st mulus flashes which we e given at 3 minute intervals In other respects the procedure was im l r to that described in F g 1 Each ERG was displayed in a high cathode ray sweep speed (lower trace) and s multaneously in a slow speed (upper trace)


BACKGROUND LIGHT INTENSITY
LOG 5.0
LOG 4.0
LOG 3.0
LOG 2.0
LOG 1.0
LOG 0
BACKGROUND LIGHT ON <1
3
BACKGROUND LIGHT OFF <1
3
6
DA
400 µV
20 ms
10 m sec

the shape and size of the ERG was different from the response recorded every 30 seconds The first positive peak of the ERG was ample and dominating and was followed by a marked negative trough which in turn was succeeded by in distinct oscillatory potentials of low amplitude

On adaptation to backgrounds of weak intensities (log $I_B = -5$ and -4) the amplitude of the oscillatory potentials increased distinctly *as compared to the* response obtained in dark adaptation (Fig 10) Further increments in back ground luminance however reduced the oscillatory potentials considerably leaving only the first 2 or 3 peaks distinguishable on the ERG

When recorded in weak background illumination (log $I_B = -5$ and -4) the summed amplitude of the oscillatory potentials also was measured to be larger than in dark adaptation (Fig 11) but when the intensity of background light further augmented there was a decrease of the summed amplitude of the oscillatory potentials On adaptation to maximal background intensity (log $I_B = 0$) the summed amplitude of the oscillatory potentials was measured to be about half of the value obtained in dark adaptation prior to light adaptation to the background

To obtain more accurate results the energy of the oscillatory potentials was calculated It likewise increased on adaptation to a weak background (log I_I = -5) and attained a maximum at a background intensity of log $I_B = -4$ (Fig 12) On adaptation to a moderate background intensity (log $I_B = -3$) the oscillatory potentials energy declined and remained low when recorded against stronger backgrounds (log $I_B = -2$ or stronger)

The dominant frequency of the very small oscillatory potentials recorded in *dark adaptation was around 145 Hz (Fig 13) On adaptation to a background* of weak intensity (log $I_B = -5$) the frequency immediately decreased to about *100 Hz There was no further change in frequency on adaptation to stronger* background intensities (log I_B -4 to 0) and the dominant frequency remained between 93–100 Hz

Fig 14 shows the implicit times for the individual oscillatory peaks on adap tation to successive increments in background luminance The transition from dark adaptation to a weak background illumination (log $I_B = -5$) seems to be associated with certain changes in implicit times Stronger backgrounds induce no systemic change in peak latencies It must be pointed out that little informa

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Fig 10

Oscillatory potentials and a and b waves recorded in dark adaptation (D A) and on adaptat n to backgrounds of d fferent intensities *Weak light adaptation* caused by stimulus flashes wh ch were given at 3 minute intervals In other respects the procedure w s s milar to that described in F g 1 Each ERG was d splayed in a high cathode ray swe p peed (lower t ace) and simultaneously in a slow speed (upper trace)

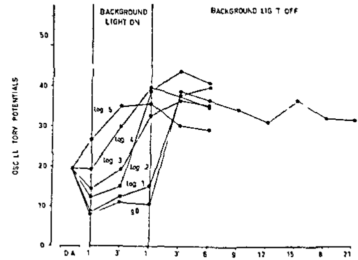


Fig 11

Summed amplitude of individual oscillatory peaks on adaptation to background light of different intensities Weak light adaptation caused by stimulus flashes Oscillatory peaks were measured in arbitrary units (mm) from ERG s recorded with the same procedure as described in Fig 10 and plotted against time scale on x axis The same calibration as in Fig 2

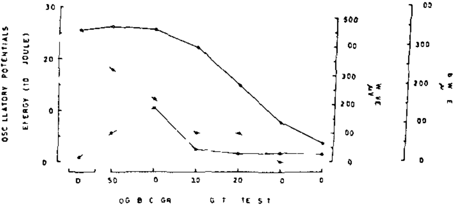


Fig 12

Calculated energy of oscillatory potentials and amplitudes of a and b waves in relation to background light of different intensities Weak light adaptation caused by stimulus flashes The energy of oscillatory potentials is calculated from ERG s shown in Fig 10 at 3 minutes after adaptation to backgrounds of different intensities Black circles energy of oscillatory potentials Open circles continuous line amplitude of a wave open circles dashed line amplitude of b wave

tion is obtained by such measurements since the b wave interferes with the oscillatory potentials and the rate of rise of the former may influence the shape and size of the latter

Recovery in the dark

When adapted to a strong background ($\log I_B = 0$) an oscillatory response showing 4 distinct peaks of large amplitude was not present until after 6 minutes of recovery in the dark (Fig 10) but a similar response was obtained only 3 minutes after adaptation to a background of $\log I_B = -2$ and when adapted to a weak background ($\log I_B = -5$) this response was evoked 1 second after the background light was switched off

After exposure to moderate background intensities ($\log I_B = -4$ to -2) the oscillatory potentials recorded at 1 second in the dark showed a prominent second peak (0) This ERG was similar to that response which shows interference with on effect and off effect (cf Nagata 1962)

After adaptation to strong background ($\log I_B = -1$ and 0) which are supposed to induce saturation of the rods the oscillatory potentials were very small when recorded within 1 second in the dark

The summed amplitudes of the oscillatory potentials further demonstrated these changes (Fig 11) When adapted to backgrounds of moderate intensity

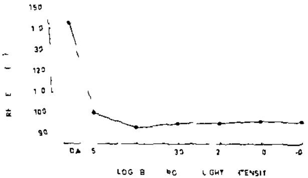


Fig 13

Dominant frequency of oscillatory potentials in relation to background light of different intensities Weak light adaptation caused by stimulus flashes The frequency is calculated from ERGs shown in Fig 10 in dark adaptation (D.A) and at 3 minutes adaptation to a background light The dominant frequency decreased from 143 Hz in darkness to less than 100 Hz on adaptation to background illumination

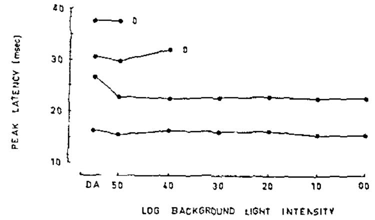


Fig 14

Peak latencies of *individual oscillatory potentials (0₁ 0 0₃ 0₄)* in relation to background of different intensities Weak light adaptation caused by stimulus flashes The values are measured from ERG s shown in Fig 10 at 8 minutes adaptation to backgrounds of different intensities The same error of measurements as in Fig 5

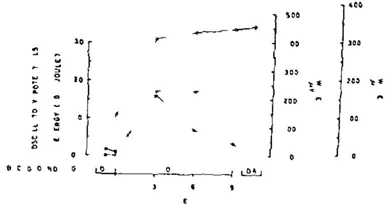


Fig 15

Calculated energy and amplitudes of a and b waves during recovery in the dark after adaptation to a background of maximal intensity (log $I_B = 0$) Weak light adaptation caused by stimulus flashes Oscillatory potentials and a and b waves were displayed simultaneously at different cathode ray sweep speeds Black circles energy of oscillatory potentials Open circles continuous line amplitude of a wave open circles dashed line amplitude of b wave

(log $I_B = -3$ to -2) the recovery in the dark of oscillatory potentials was extremely rapid and their summed amplitude was a large figure within 1 second in the dark The summed amplitude of oscillatory potentials reached a

maximum within 3 minutes after adaptation to a background of any intensity It was remarkable that after adaptation to a background illumination for 6 minutes the oscillatory potentials recorded during the first 3–9 minutes in the dark had a considerably larger amplitude than those recorded in dark adaptation prior to the exposure to backgrounds in response to flashes given at 3 minute intervals

The energy of the oscillatory potentials adapted to the strongest background luminance used (log $I_B = 0$) was calculated After cessation of the background light the regeneration of the oscillatory potentials was facilitated and after 3 minutes in the dark the energy of the oscillatory potentials had reached a maximal value (Fig 15) After that a uniform decline was observed which lasted for 21 minutes or more

Frequency

The changes in oscillatory energy were accompanied by characteristic alterations in dominant frequency of the oscillatory potentials When the background light was on the dominant frequency was around 100 Hz and remained so during the first 3 minutes in the dark or as long as the oscillatory potentials gained in amplitude (Fig 16) At 6–9 minutes in the dark as the energy of the

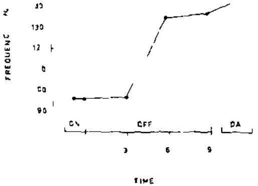


Fig 16
Dominant frequency of oscillatory potentials during recovery in the dark after adaptation to a background of maximal intensity (log $I_B = 0$) Weak light adaptation caused by stimulus flashes The procedure for recording was the same as described in *Fig 15* The dominant frequency increased from 96 Hz to 145 Hz on adaptation to darkness

oscillatory potentials decreased the dominant frequency changed to 135-145 Hz

The implicit time of the first two oscillatory peaks (0_1 0_2) changed very little during the recovery in the dark after adaptation to the strongest background ($\log I_F = 0$) (Fig 17) Within 3 minutes after the background light was switched off the 3rd (0_3) and 4th (0_4) peak appeared The peak latencies of 0_3 and 0_4 decreased during the first 6 minutes of dark adaptation The interval between the 2nd and 3rd peak (0_2–0_3) decreased about 3 msec and the interval between the 3rd and 4th peak (0_3–0_4) was shortened about 4 msec. The interval between the first and last peak (0_1–0_4) also decreased around 4 msec which was demonstrated as an increase in frequency by means of Fourier analysis (Fig 16)

The a wave

When recorded in response to flashes given at 3 minute intervals the amplitude of the a wave did not decrease significantly on adaptation to a weak background light ($\log I_F = -5$ and -4) (Fig 12) The a wave was reduced about 15 % in background light of moderate intensity ($\log I_B = -3$) On adaptation to the strongest background ($\log I_F = 0$) the a wave decreased to about

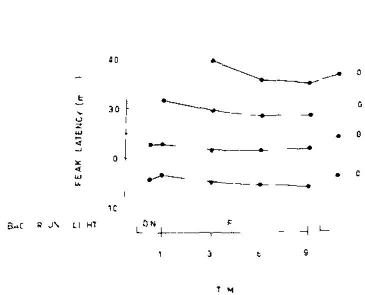


Fig 17

Peak latencies of individual oscillatory potentials (0_1 0 0 0_4) during recovery in the dark after adaptation to a background of maximal intensity ($\log I_B = 0$) Weak light adaptation caused by stimulus flashes The procedure for recording the FRC was described in Fig 15 The same error of measurements as in Fig 5

0 μV which corresponded to less than 15 % of its value in dark adaptation (160 μV) The curve obtained when the a wave amplitude was plotted against log background intensity was similar to that depicted in Fig 3 where light flashes were given every 30 seconds

When adapted to the strongest background light (log $I_B = 0$) the recovery of the a wave was almost completed after 3 minutes in the dark (Fig 15) No break (alpha point) on the a wave recovery curve was present

The b wave

The b wave sensitively adapted even to a weak background intensity (log I_P = 5) which actually reduced the b wave amplitude about 30 % of its value in dark adaptation (Fig 12) On adaptation to stronger backgrounds the b wave further decreased fairly uniformly and no b wave was seen above the iso electric line when recorded in strong background light (log $I_B = -1$ and 0)

The recovery of the b wave in the dark was slow and after 21 minutes in the dark only about 75 % of its value in dark adaptation was attained (Fig 15) The influence of the flashes given every 3 minutes might have delayed the re covery After around 6 minutes in the dark there was probably a break in the recovery curve (alpha point)

Discussion

These experiments show that the oscillatory potentials adapt differently from the a wave and b wave of the human ERG The frequency of stimulation by strong flashes has a decisive influence on the amplitude of the oscillatory po tentials when recorded in darkness or against weak backgrounds This is pre sumably explained by the fact that the light adaptation caused by the flashes will vary with the stimulation frequency For example repetitive flashes delivered every 30 seconds in dark adaptation evoke much larger oscillatory potentials than flashes given at 3 minute intervals single flashes elicit very small if any oscillatory potentials

A weak background illumination (log $I_P = -5$ or -4 in the experiments) seems to facilitate the regeneration of oscillatory potentials when flashes are given at long intervals as compared to the response recorded in dark adapta tion (Fig 1?)

Interestingly at this weak background luminance which does not bleach any

significant fraction of photopigments (log $I_B = -5$ in this study) there was also a distinct change in the dominant frequency of the oscillatory potentials When recorded in dark adaptation the frequency was around 145 Hz and decreased suddenly to 90–100 Hz on adaptation to this background This luminance corresponds to the level where cones begin to function (cone threshold)

It is known from psychophysical investigations that the scotopic luminosity curve holds below a background luminance of 10^{-3} candelas/m (Walters & Wright 1943 LeGrand 1968) Above that luminance the Purkinje shift is supposed to occur It has also been demonstrated that the maximal spectral sensitivity of the human eye changes from short wavelengths (blue) to long wavelengths (yellow) at a background luminance of about 10 candelas/m (van Lith 1966) This corresponded approximately to log $I_I = -5$

The Purkinje shift was not determined and since its occurence is dependent on several factors (see Mandelbaum & Nelson 1960) it is not known where it actually occurred in this experiment During adaptation to darkness however the reverse change in the dominant frequency of the oscillatory potentials was encountered *i e* the transition from low to high values This change did not occur until the b wave had regained part of its amplitude

When flashes were given at long intervals (3 minutes) the oscillatory potentials recorded in dark adaptation had a low amplitude and a high frequency In mesopic conditions the oscillatory potentials were much larger and had a lower frequency

The frequency change of the oscillatory potentials probably reflects some basic alteration in the activity of the inner nuclear or internal plexiform layer of the retina Several events are known to occur in these layers on adaptation to light or darkness For example slow rod responses evoked by weak blue stimuli are excluded from ganglion cells when rapid cone signals arrive (Gouras 1966 Gouras & Link 1966) Amacrine cells seem to accentuate the changes in retinal sensitivity in response to varying illumination (Werblin & Dowling 1969) The reorganization of receptive fields of the ganglion cells on adaptation to light or darkness is well known (Kuffler 1953 Barlow Fitzhugh & Kuffler 1957 Henn & Grusser 1969) Morphological studies suggest that cone and rod signals could follow separate pathways through bipolar and amacrine cells layers (Boycott & Dowling 1969)

There was a remarkable decline of the energy of the oscillatory potentials when the background luminance was increased to about 1 candela/m (log $I_B = -3$) The ERG recorded at this background showed only a photopic b wave (Fig 10) But an a wave of comparatively large amplitude was still present The oscillatory response showed that the last two peaks (0_3 0_4) were depressed At this background luminance the maximal spectral sensitivity of the b wave

of human ERG is known to change from a scotopic to a photopic luminosity curve (van Lith 1966)

It is possible that a part of the decrease of oscillatory energy is simply a result of the reduction of the size of the total ERG response and especially of the scotopic b wave When the sensitivity of the photopic b wave becomes higher than that of the scotopic b wave the oscillatory potentials decrease Since in mesopic conditions the ERG contains much rod activity it cannot be ruled out that some influence from rods into the inner layers of retina might affect the regeneration of oscillatory potentials Algvere & Westbeck (1972) studied the oscillatory potentials during adaptation to darkness in response to flashes given at a certain stimulation pattern The oscillatory potentials recorded in dark adaptation were larger than those in mesopic range (*cf* Adams & Dawson spectral sensitivity of oscillations in mesopic conditions)

At a strong background illumination the rods become saturated (Aguilar & Stiles 1954 Rushton 1961) This phenomenon seemed to be present at the strongest backgrounds (log $I_B = -1$ or 0) corresponding to $1.2 \times 10^{3.4}$ scotopic trolands There was no appreciable change in the energy or frequency of the oscillatory potentials when passing the rod saturation which on appropriate bleaching time will reduce the concentration of photopigments less than 10% (Rushton 1965 a b c d e 1966) The retinal response recorded at this background has a small a wave and a b wave of short duration thus having the appearance of a pure photopic ERG The oscillatory potentials recorded were small whether light stimuli were given at long or short intervals

The 3 components of the ERG studied showed characteristic differences in their rates of recovery in the dark After adaptation to bright backgrounds the a wave recovered rapidly but the b wave gained very slowly in amplitude When recorded in response to flashes given at 3 minute intervals the oscillatory potentials amplitude increased during the first 3 minutes in the dark and after that it declined The rapid recovery of the oscillatory potentials was also described by others (Genest 1964 De Molfetta Spinelli & Polenghi 1968)

When flashes were given every 30 seconds however the oscillatory potentials gained much more in amplitude during the first 5 or 6 minutes in the dark and were recorded with such large amplitudes on further adaptation to darkness as well Then a large a wave was present in response to the flashes of light the colour temperature of which corresponded to about 6500 K The question arises whether active rods might influence the regeneration of oscillatory potentials in mesopic or scotopic conditions Adams & Dawson (1971) studied a fast retinal potential (FRP) of the human eye related to the oscillatory potentials in response to stimuli of equal energy Interestingly in mesopic conditions the FRP was much larger when elicited by stimuli of 500 nm than recorded in

response to 560 nm (or longer) wavelengths If so some input from the rod system into the regeneration of the oscillatory potentials must occur On the other hand in photopic conditions Adams & Dawson found that the oscillatory potentials showed a photopic spectral sensitivity as was also reported by Rouher Sole & Alfieri (1966)

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COMPARISON BETWEEN STEREO AND SLIT IMAGE PHOTOGRAMMETRIC MEASUREMENTS OF THE OPTIC DISC

BY

C E T KRAKAU and K TORLEGÅRD

The volume of a normal optic disc has been measured with the stereo photogrammetric technique and with the slit image method The measurements indicate that these two methods give similar precision

Key words optic disc – stereophotogrammetry – slit image photogrammetry

Observation of the papillary shape has been a sign of great clinical value since the early days of ophthalmoscopy There are also early attempts to estimate qualitatively the size and shape of the papilla but it is only in the comprehensive glaucoma studies of the past few decades that measurements have begun to be performed (Piccard 1948) Several of these investigations make use of such measures as the cup/disc ratio These methods have their obvious limitations such as arbitrariness in defining the limits of the cup on a fundus photograph or during ophthalmoscopy

For a more complete and accurate description of the papillary shape and size some kind of three dimensional presentation seems inevitable Level measurements in the eye ground by means of stereophotographs have been described by Krakau (1956) and by Bynke & Krakau (1960) The highly advanced stereophotogrammetric technique which cartographers use for drawing

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maps showing differences in altitudes etc can be applied to stereophotographs of the eye ground with quite satisfactory results This technique has been used by Crock (1970) who describes it at length One drawback is the need for special tools and for trained personnel to evaluate the pictures which makes the method quite expensive For this reason a technique was developed (Holm & Krakau 1969) making use of photographs of the optic disc which is illuminated by a number of parallel slits

It was found useful to compare the precision of these two methods by applying them to the same optic disc

Methods

A) EXCAVATION MEASUREMENTS BY MEANS OF STEREOPHOTOGRAMMETRIC TECHNIQUE

The series of stereophotographs used in the present investigation was obtained with the Zeiss fundus camera to which the Allen stereoscopic separator was adapted A pair of stereophotographs consists of one picture exposed through the right part and another through the left part of the pupil In the set up used two consecutive exposures have to be made to obtain the stereo pair The pupillary size limits the base length between the stereo images In the present series the base was set at 3 mm on the separator For the evaluation the two images are placed in a photogrammetric plotting instrument where a three dimensional model of the photographed object is reconstructed stereoscopically from the two pictures The operator looks into the stereoautograph at a three dimensional image of for instance the eye ground and he has the means to move a small floating mark in space The movement of this mark can be recorded on counters in an orthogonal 3 D coordinate system The movements can also be transferred to a drafting table where two of the three coordinates are represented graphically while the third is given as contour intervals cross sectional distances or spot elevations The operator moves this mark on the eye ground with a fixed elevation and the line representing this level may be drawn by moving the mark across the eye ground From a number of such contour lines it is possible to estimate cup volumes etc Alternatively the operator may follow the surface in some fixed direction which crosses the papilla During this movement he adjusts his mark to remain on the surface and drafts a cross section of the papilla This is the procedure followed in the present series since the sections so obtained can be directly compared with those of the slit method Parallel sections through the papilla drawn in a Wild A 7 stereo autograph are shown in Fig 1 The spacing of the sections is of course arbitrary in this instance eight sections cross the papilla

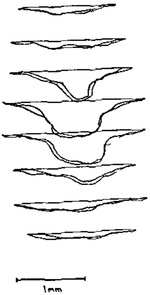


Fig. 1

Sections through a disc drawn from a pair of stereophotographs in a comparator. The sections have been followed twice. Depth not calculated in absolute units.

The surface enclosed by the line following the bottom of the papilla and by the line connecting the points at the upper and lower borders of the papilla is measured on each of the sections – planimetrically or directly. A volume measure is obtained by adding the sections according to Simpson's rule or the trapezoid rule.

The precision of the method has been evaluated by repeated measurements of the excavation volume in relative units on the same pair of images and by measurements on a series of four pairs of images of the same papilla. Volume values in absolute units can be calculated after a photogrammetric calibration of the camera. Moreover, corrections have to be made for the refraction of the eye photographed.

The precision of measurements on the same pair of images gave a coefficient of variation of 3 per cent ((repeated measurements on 4 pairs) of the volume measure, which is very satisfactory. Measurements on different pairs gave a considerably higher coefficient of variation, or 5 per cent. This result is not surprising considering that the two images in the pair are not made simultaneously. The fixation stability is therefore crucial since this influences the

measuring base and the angular orientation of the camera in relation to the eye It is concluded that when using the stereophotogrammetric method one should either make the two images in one exposure or make them at so short an interval that the effect of a slight eye movement can be ignored (Parel et al 1968)

B) EXCAVATION MEASUREMENT BY MEANS OF THE MULTIPLE SLIT METHOD

A system of equidistant light slits is projected over the object to be measured and the slit images on the surface of the object are photographed The slits are vertical and the axes of the slit projector and the camera make an angle on a horizontal plane If the object protrudes or is excavated the slits crossing it will show deviations from the vertical on the photograph (Fig 2) A reference plane can be defined and the areas of the deviations of slit images over this plane can be measured planimetrically From our knowledge of the geometry at photography the volume of the protrusion or excavation can be estimated in absolute measure

This principle has been applied to the present problem a number of vertical light slits have been projected on to the papilla and an eye ground photograph has been taken

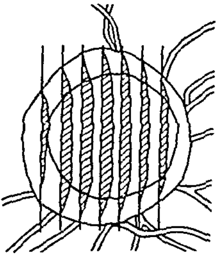


Fig 2
Schematic drawing of slits imaged on the disc The slit images follow the bottom of the cup The surfaces of the sections used for estimation of the cup volume are hatched

Apparatus

A slit lamp camera is used in combination with a Goldmann contact lens (-64.5 dpt). In the plane of the original single slit a glass plate is placed containing a pattern of parallel opaque lines with clear slits in between. In the eye ground the spacing of the slits is 0.23 mm. Six or seven slits will cross on the disc.

The original biomicroscope camera unit was not suitable for optimal adjustment and focusing of the image and was therefore replaced by a mirror reflex ground glass camera. Since both ingoing and outgoing rays have to pass through the pupil the angle between projector and camera axes has to be small. In the present set up it has been set at 15 degrees.

Operation

The pupil has to be at least 5 mm in diameter. As a rule five or six photographs are taken in sequence. The multiple slit images were measured in a simple device consisting of a low power magnifier the eyepiece of which was provided

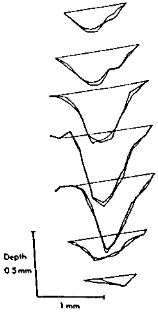


Fig. 3

Section drawn from a slit image. The contours have been drawn twice.

with a small central spot and a cross table movable in two orthogonal directions by micrometer screws The film was placed on the cross table and the section lines were redrawn by moving the cross table so that the mark of the eyepiece followed them on the film negative The surface included between the base line drawn over the papillary borders and the line on the bottom of the papilla was measured

Fig 3 shows two different measurements of the same image of a papillary excavation In view of the fact that the lines are often rather blurred the two lines follow each other remarkably well

The results of four measured photographs of the same papilla as before are superposed in Fig 4 On the ordinate axis is put the surface of the sections in arbitrary units on the abscissa is indicated the localization of the sections These are all parallel As we should expect the slits fall in different places at each exposure but obviously the surface values for the different sections fit in well on a common curve The integral of the curve outlined represents the volume of the cup By applying some suitable rule as in method a) this is calculated approximately and in relative units from the values of the sections It is

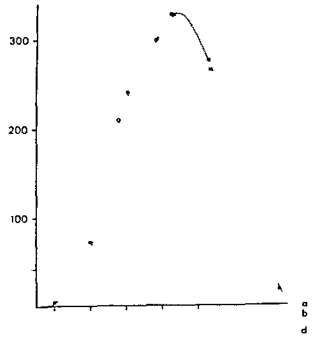


Fig 4

Surface values plotted in arbitrary units (ordinate axis) against their localisation on the disc for four images The grids fall at random on the disc but the sections of each picture (a b c d) are equally spaced

possible to convert these units to absolute ones As a rule there is no need for a correction with reference to the refractive state of the eye since as was pointed out by Goldmann (1967) the magnification in an eye with the contact lens (-61 5 dpt) is practically unchanged in a wide range of refraction

The dispersion of the volume estimates obtained by the slit method by repeated measurements on the same photograph was less than two per cent When different photographs of the same papilla were measured the dispersion (coeff in variation) of the volume estimates was 2 2 per cent (number of photographs = 6) In the original (1969) version of the method the photographs were projected on a paper and the sections drawn and planimetered This procedure is less accurate than direct measurements on the negative

Discussion

The measurements of the two series just described have been made in as similar a way as possible the same disc has been measured the measurements have been made in sections in the stereophotogrammetric method as in the slit method the number of sections crossing the disc has been about the same in the two methods

In both methods it is the surface of the nerve fibre layer that gives the section line The definition of this surface is sometimes difficult in the stereoscopic method In the slit method some blurring of the slit images can be attributed to the fact that light penetrates into this layer

In the present normal case the two methods gave an equivalent quality of measurement at repeated measurements on the same images Provided the two stereo images are taken simultaneously or at very short intervals it is likely that this also holds true when measurements are made on a series of pictures of the same disc

The good quality of measurement with the methods treated above is obtained at the cost of considerable labour This is a drawback when applying them to extensive population studies It is also questionable whether the investment of so much work is rewarded in such a type of investigation In the population studies by Armaly (1967) and by Becker (1970) the simple c/d ratios estimated in the ophthalmoscope or on fundus photographs have been used Groups of normals glaucomatous cases or glaucoma suspects give wide distributions of the c d ratio overlapping to a great extent

The more precise method of multiple sections has also been used for this purpose by Helm et al (1972) But even in this investigation there is a considerable overlapping of the groups which is by no means surprising Com

pletely normal eyes may have considerable excavations as is well known and the glaucoma group necessarily contains cases of different stages of development from normal to more or less complete excavations Thus though the dispersion of the estimates by random errors of the method is great the distribution we want to describe is much wider and therefore an improvement of the method cannot be expected to give a much better separation of the groups

The precise methods come to the fore in a different type of investigation namely those in which repeated measurements are made at intervals on the same patient By such investigations we can approach important glaucoma problems for instance those concerning the effect of pressure on the excavation or the relation between the development of the excavation and the visual field defects For repeated measurements on the same individual there is generally no need to convert the values into absolute units

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UNEQUAL AXIAL LENGTH OF EYEBALL AND OCULAR TENSION

BY

A TOMLINSON and C I PHILLIPS

In 13 anisometropes aged 8–16 years measurements were made of refractive error ocular tension and various ocular dimensions including axial length by ultrasound The eye with the greater axial and vitreous length had the significantly higher ocular tension

Key words intraocular tension – eye axial length – ultrasonography – anisometropia

Tomlinson & Phillips (1970) examined groups of individuals with different refractive errors and found a statistically significant positive correlation between axial length and ocular tension i e a tendency for a long eyeball to have a relatively high ocular tension and a short eyeball to have a low tension This is consistent with the findings of Wallace & Lovell (1969) and Tomlinson & Phillips (1970) that applanation tension was highest in myopes and lowest in hypermetropes with emmetropes intermediate Abdalla & Hamdi (1970) found ocular tension in myopes higher than in emmetropes Bengtsson (1972) however found no difference in ocular tension of different refractive groups when allowance was made for the influence of blood pressure sex season and time of day

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In all such investigations it is impossible to achieve groups of individuals who are absolutely identical save for the property being studied Since the eye is a paired organ the best possible control for sex season time of day blood pressure etc would be a fellow eye hence the present study of anisometropes

Material

Thirteen anisometropic children aged 8–16 years were chosen from a large number attending a School Eye Service Clinic Eight were female and five male

Methods

Both eyes were examined in all cases The toss of a coin decided which eye was examined first in five cases the more myopic/less hypermetropic was first and in eight the less myopic/more hypermetropic was first *Applanation tensions were done by an independent observer with a Haag Streit 900 slit lamp microscope he was not aware of which was the larger eyeball The following ocular dimensions were recorded for all subjects

I) Corneal radius measured with a movable mire keratometer
II) Corneal thickness measured with the Type I attachment for the Haag Streit slit lamp
III) Depth of the anterior chamber measured with the Type II attachment
IV) Lens thickness
V) Length of the vitreous chamber

(IV and V) measured from an anterior posterior axis trace of the eye obtained by A scan ultrasonography

VI) Axial length of the eyeball found from the addition of III) IV) and V)

Ocular tensions were compared by the Wilcoxon matched pairs signed ranks test (Segal 1956) which is particularly appropriate when measurements are done on the two eyes of the same individual (almost an ideal matched pair)

* A much better way of ensuring exactly a one to one allotment with minimum sacrifice of randomness would have been to toss a coin for *alternate* cases the first in a series of two would be a random choice (*say right*) the second would automatically follow (left)

Table I

A comparison by the Wilcoxon matched pairs *signed ranks test of the ocular tensions of the two eyes of 13 anisometropes aged 8–16 years*

Eye 1 is the eye with	Steeper corneal radius	Deeper anterior chamber	Thicker lens	Longer vitreous chamber	*Longer* axial length	Greater amount of relative myopia	First measurement of tension
Mean ocular tension of eye 1 *(mmHg)*	13.92	13.92	13.46	14.15	14.15	14.00	13.46
Number of matched pairs with a sign N =	9	7	8	9	9	9	9
Value of T =	13	7.5	14.5	5	5	10.5	15.5
Level of significance	0.216	0.27	0.62	0.05	0.05*	0.124	0.34
Mean ocular tension of eye 2 (mmHg)	13.38	13.38	13.85	13.15	13.15	13.31	13.85
Eye 2 is the eye with	Flatter corneal radius	Shallower anterior chamber	Thinner lens	Shorter vitreous chamber	Shorter axial length	Smaller amount of relative myopia	Second measurement of tension

Results

Statistically significant The eye with the greater axial length in a pair had the higher ocular tension ($p < 0.05$) mean of 14 15 mmHg compared with 13 15 mmHg Not surprisingly the eye with the greater length of the vitreous chamber of a pair also had the higher ocular tension ($p < 0.05$)

Non significant results Although there was a tendency for the more myopic eye of a pair to have the higher tension this was not enough to be significant – as opposed to the situation with axial length mentioned above ($p < 0.13$)

Other non significant comparisons were made of ocular tensions in relation to corneal radius depth of anterior chamber lens thickness and order in which eyes were examined

Discussion

This study of anisometropes probably constitutes better evidence than our previous study (Tomlinson & Phillips 1970) that a greater axial length of the eye ball is associated with a higher ocular tension while a shorter axial length is associated with lower ocular tension By chance (toss of coin) the shorter eye was examined first in nine cases and the longer in four (non significant difference from expected 6 5 6 5 ratio $p = 0.26$) This is greater than the 8 5 ratio based on refraction (see Methods) because one patient s more myopic eye had a shorter axial length than the fellow eye Any distortion of our results thereby introduced would tend to discriminate *against* the significant difference we have observed since the second eye to be applanated often tends to have a lower pressure (Bankes et al 1968 Leighton & Phillips 1970) although Hollows & Graham (1966) found mean pressures to be identical with the Schiotz tonometer lower readings for the second eye have been reported for example by Harrington (1959) but some observers report no difference for example Armaly (1961)

We think that emmetropisation in spite of varying axial lengths (Sorsby et al 1957) explains the lack of significance of an association between refractive error and ocular tension – larger numbers would probably produce a significant result however Bengtsson s (1972) use of refractive error and not axial length is not likely to be an explanation for his negative findings since he examined large numbers of patients with varying refractive errors – but he eliminated the influence of sex season time of day and blood pressure Our examination of anisometropes provides the ideal control for these factors and we have no satisfactory explanation for his findings which are different from ours (Tomlinson & Phillips 1970) and from the results of others who have measured

ocular tension in patients with different refractive errors (Wallace & Lovell 1969 Abdalla & Hamdi 1970) It is of some interest in the context of Bengtsson s finding of the importance of blood pressure, that Leighton & Phillips (1972) have found a significant tendency for patients with open angle glaucoma to have higher blood pressures than patients with normal ocular tensions

Acknowledgment

We wish to record our thanks for a grant for equipment from the Wellcome Trustees

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ANTERIOR CHAMBER CLEAVAGE SYNDROME
Atypical Case of Peters Anomaly with Primary Aphakia

BY

J HOLMARK and O A JENSEN

An otherwise healthy girl had from birth right sided microphthalmia with leukomatous cornea and left sided staphyloma centrally on a leukomatous cornea surrounded by a deep blue sclera The intraocular pressure was raised and the staphyloma increased in size The eyeball was enucleated at three months of age and showed anterior chamber cleavage syndrome The corneal stroma was replaced by connective tissue No Bowman s membrane was found and the Descemet s membrane was present only as small coiled remnants centrally No lens was observed The iris was seen only in a few sections as a string attached to the cornea The posterior part of the eye was normal
The classification of the case is discussed and it is concluded that it can be considered an advanced atypical case of Peters anomaly with the rarely seen primary aphakia and combined with Rieger s dysplasia

Key words anterior chamber cleavage syndrome – malformations – Peters anomaly – aphakia primary

Faulty cleavage of the anterior chamber may lead to changes in the cornea and anterior chamber of varying degrees Various clinical pictures result from

Presented by O A Jensen at the 11th Meeting of the European Ophthalmic Pathology Society H lsink Jun 19
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these changes (Alkemade 1969 Reese & Ellsworth 1966) The case presented below is considered to represent an advanced atypical case of the special form of faulty cleavage of the anterior chamber called Peters anomaly or mesodermal dysgenesis of the cornea (Alkemade 1969) and is further unique by the absence of the lens

Material and Methods

Clinical history

A 3 month old girl presented with connatal malformations of both eyeballs She was No *3 of 3* of which the eldest had degeneration of the left acoustic nerve Otherwise there was no family disposition No consanguinity Pregnancy and delivery were normal No drug or radiation exposition during pregnancy Birth weight and length were normal

A detailed clinical and laboratory examination revealed no anomalies of other organs The face was normal but she had abundant lanugo down to the eyebrows on the auricle down the back over the shoulders and over the sacral region Examination by ophthalmologists shortly after delivery showed microphthalmia on the right side with leukomatous cornea and numerous vessels and on the left side a staphyloma

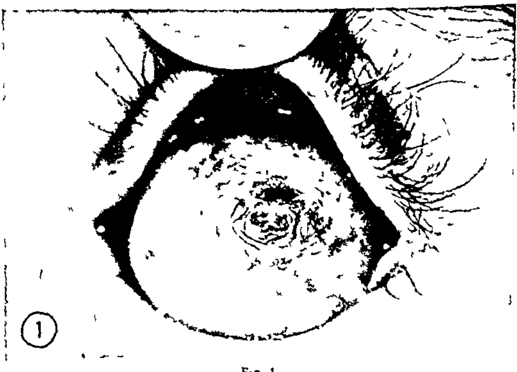
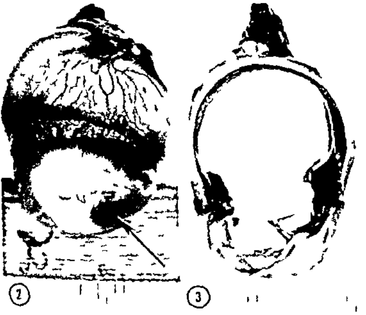


Fig 1
Clinical appearance of the left eye at the age of 3 months Note the paracentral ulcer

centrally on the leukomatous cornea which was surrounded by a deep blue sclera (Fig 1) The intraocular pressure was 30 mmHg Because the staphyloma increased in size eventually involving the whole cornea and making closure of the eyelids impossible the left eyeball was enucleated No trauma or perforation was reported or observed Anti laucomatous operations were later performed on the right eye The intraocular pressure of this is now normalized and light perception is preserved

Histopathological method

The enucleated eyeball was fixed in 4 per cent buffered neutral formaldehyde for 24 h urs at 4 C Routine paraffin technique was employed D paraffinized hydrated sections were stained by routine stains PAS alcian blue, by several metachromatic methods and by Congo red



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The enucleated eyeball The whole cornea was taphyl matou and n n transpa ent Note the small ulcer (arrow)

Fig 3
The sectioned eyeball No lens or iris diaphragm is seen Strings are runn ng backwards from the thick part of the cornea towards the ciliary region

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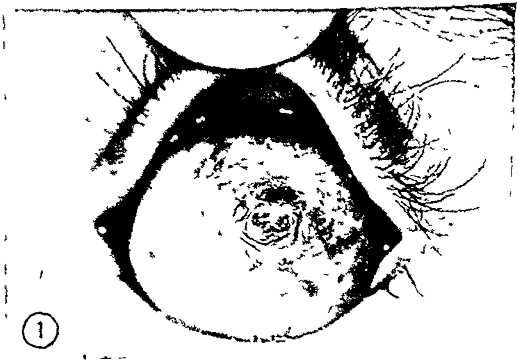


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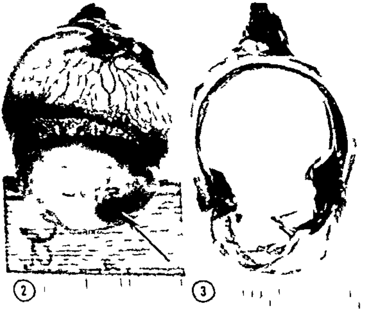


Fig 2
The enucleated eyeball The whole cornea was staphylomatous and non transparent Note the small ulcer (arrow)

Fig 3
The sectioned eyeball No lens or iris diaphragm is seen Strings are running backwards from the thick part of the cornea towards the ciliary region

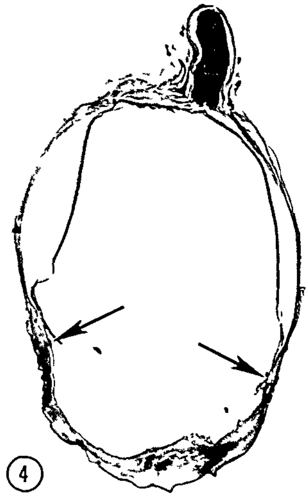


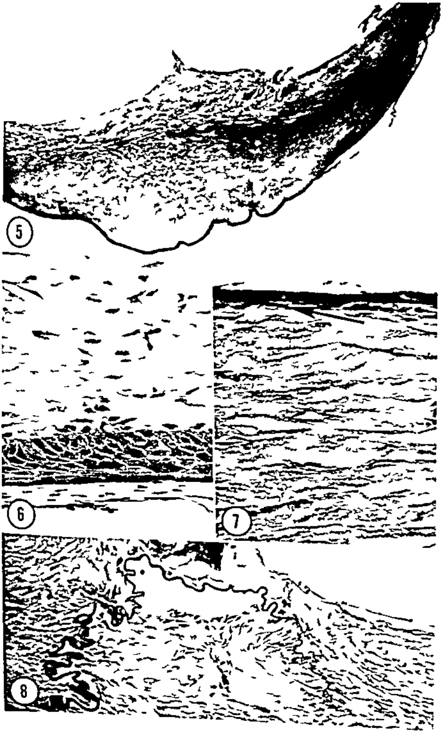
Fig 4
Survey of histological section Note the enormous thickness of the cornea centrally The ciliary regions marked by arrows (x 4)

Fig 5
Section through the staphyloma The corneal stroma is replaced by connective tissue with small vessels (x 10)

Fig 6
Anteroir surface of staphyloma Heavy keratinization and absence of Bowman s membrane is noted (x 2/5)

Fig 7
Posterior surface of staphyloma Descemet s membrane is absent A very atrophic iris stroma and pigment epithelium are seen (arrow) (x 275)

Fig 8
Coiled remnants of Descemet s membrane (PAS x 100)


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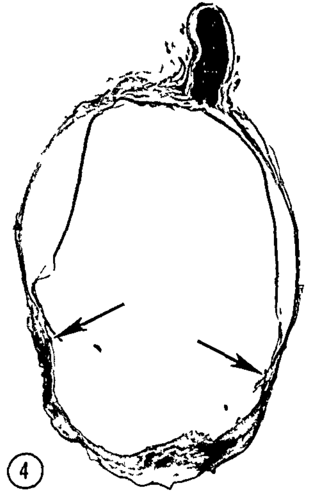


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Fig 7
Posterior surface of staphyloma Descemet s membrane is absent A very atrophic iris *stroma* and pigment epithelium are seen (arr w) (x 27)

Fig 8
Coiled remnants of Descemet s membrane (PAS x 100)


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Results

(Oft pat Lab No 691/71) The length of the enucleated left eyeball was increased (25 mm) The whole cornea was staphylomatous and measured 16 x 12 x 10 mm (Fig 2) Sectioning showed the thickness of the cornea to vary up to a maximum of 4 mm (normal about 0 6 mm) (Figs 3 4) *No iris lens or* remnants of lens were seen In the upper part of the staphyloma a small ulcer *was noticed (Fig 2)*

Microscopical examination revealed the whole posterior part of the eye to be normal only the anterior segment was pathologically changed Normal corneal stroma was not seen but was replaced by a dense connective tissue with numerous vessels and a few inflammatory cells peripherally (Fig 5) The staphyloma was covered by a heavily keratinized epithelium (Fig 6) No Bowman s membrane or endothelium was observed (Figs 6 7) In a few sections small remnants of a coiled Descemet s membrane were found (Fig 8) The posterior side of the staphyloma was covered by a thin pigmented layer (Fig 7) in a few places separated from the connective tissue by a homogeneous basophilic substance and small masses of tissue resembling smooth muscle tissue (Fig 9) Further in some sections a very atrophic iris stroma covering the inside of the staphyloma was seen (Figs 7 9) We regard these structures as a dysgenic iris firmly attached to the inside of the staphyloma No chamber angle structures were observed Centrally where the staphyloma was thickest a mass of basophilic substance and proliferating pigment epithelium was found (Fig 10) From this area fine fibrils ran backwards towards the elongated ciliary processes and the atrophic ciliary body Serial sections through the ulcer revealed no perforation but the connective tissue was very thin No remnants of the lens or scar tissue in this area were noticed and no strings of uveal tissue were attached to it (Fig 11) The special stains gave *results corresponding to* connective tissue The remnants of Descemet s membrane were strongly PAS positive No amyloid was detected

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Fig 9

Small remnants of iris muscle (arrow) and iris stroma (double arrow) (x 100)

Fig 10

Proliferating *pigment epithelium centrally with strings running backwards* (x 40)

Fig 11

Section through the thinnest part of the small ulcer Note no signs of perforation or remnants of attached tissue on the posterior side (x 20)

with Peters anomaly and congenital aphakia An aphakia cannot therefore be said to be evidence against this anomaly The question in our case is whether the aphakia is primary or whether a lens had been extruded through the thin stromal part overlying the small ulcer Serial sections through this area revealed no signs of a rupture or scar Had a lens been extruded we would have expected strings or remnants of uveal tissue running towards this thin part and not, as is the case attachment of strings or fibres to the thickest part of the malformed cornea

Concerning the dysgenic iris and chamber angle they are in our opinion part of the faulty cleavage and so to some extent a Rieger s syndrome is also present. But the corneal changes are the essential ones and we consider the iris changes to represent a certain degree of Rieger s dysplasia in combination with Peters anomaly as previously described in a few cases (Alkemade 1969 Goder & Velhagen 1972)

In conclusion we consider this case to be an advanced rare case of malformation of the anterior ocular segment without formation of a normal cornea without formation of a lens and with secondary changes in the chamber structures

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Discussion

Malformations of the anterior segment of the eye concentrate around two syndromes affecting mainly the cornea (Peters anomaly dysgenesis meso dermalis corneae) and the iris (Rieger s syndrome dysgenesis mesodermalis iridis) (Alkemade 1969) Since the boundary between them is not sharp and the more or less advanced affections result in various clinical pictures the term anterior chamber cleavage syndrome as a collective name for all these changes was introduced by Reese & Ellsworth (1966) Although as pointed out by Alke made (1969) who opposed the term *faulty* cleavage syndrome of the anterior chamber was a more exact designation we consider the former to be an ap propriate term For a further description of the various anomalies as well as a discussion of etiological aspects the reader is referred to the above mentioned writers and to Goder & Velhagen (1972)

The present case gives rise to two questions

First, is the incorporation of the case into the group of Peters anomaly justified and secondly is the aphakia to be considered as primary?

The original description by Peters (1906 1908 1912) included a congenital central corneal opacity based on a defect of the deepest stromal layers with local absence of Descemet s membrane In cases described later the affection had often been accompanied by more extensive malformations of the anterior segment In the cases studied histopathologically by Goder & Velhagen (1972) Hamburg (1963 1965 1966) Manschot (1966) and Nakanishi & Brown (1971) peripheral parts of the Descemet s membrane were preserved and normal Bow man s membrane was intact in the cases of Hamburg and Manschot and even markedly thickened in Manschot s case while it was absent centrally in the cases studied by the remaining writers The present case shows no Bowman s membrane at all but small coiled remnants of Descemet s membrane The sug gestion by Manschot (1972) that these remnants might be remnants of the lens capsule appears to us not to be justified since they are too thin and resemble more closely the structure of a Descemet s membrane We therefore consider this case to be an example of far advanced dysgenesis of the cornea where the whole corneal stroma is replaced by connective tissue Whether it should be called an atypical case of Peters anomaly will always be a matter of dispute but we have not found a better designation

Concerning the aphakia a lens or lens remnants were present in the above mentioned cases taken from the literature and a cataract is not even mandatory for Peters anomaly (Goder & Velhagen 1972) According to Waardenburg (1961) aphakia associated with Peters anomaly is certainly an extreme case The only cases known to us were described by Vogt (1931) in three siblings

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RECORDINGS OF APPLANATING FORCE AT CONSTANT INTRAOCULAR PRESSURE

II Procedures applied on living human eyes

BY

WILLIAM THORBURN

The apparatus described previously in paper I is used for continuous measurements on living human eyes Methods for estimating the volume pressure relationship and changes in intraocular volume due to the content of blood and of aqueous humour are developed Typical recordings are presented.

Key words applanation – constant intraocular pressure – force recording – intraocular pressure – intraocular volume – volume pressure relationship

The apparatus previously described(15) makes it posible to measure continuously the applanating force at constant P_t This paper deals with methodological considerations in the use of the apparatus in measurements on living human eyes

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Abbreviations
P_t intraocular pressure during the experiment
P_a applanation tonometry final reading

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Methods

After anesthetizing the cornea with oxibuprocan (Novesin® Wander) 0.4% and staining with fluorescein the intraocular pressure is measured by a Draeger handheld applanation tonometer in the sitting position. P_{a1} stands for the first reading. Readings are performed during about ten minutes until there is no further essential change. P_{a} stands for the final reading. In studies using both eyes the right eye is always examined first.

All recordings of applanating force are performed with the subject in the sitting position. Two main techniques are used, namely with ascending pressure steps and with descending pressure steps. Applying ascending pressure steps, which is the basic technique, the recording is performed as follows. The undisturbed eye is fixed on a distant mark. Refractive errors are corrected in order to avoid accommodation. The pressure in the pressure chamber is set to a value according to the calibration of the apparatus which corresponds to 6 mmHg added to P_{a}. This preset P_t is continuously recorded on a two channel stripchart recorder. The applanating surface is brought in contact with the cornea and its central position is carefully observed by means of blue light and fluorescein and if necessary adjusted. The servosystem is started and the applanating force is continuously recorded. After about 3 minutes the P_t is increased 4 mmHg and the recording is continued about 3 minutes further. The P_t is then increased another 5 mmHg and the recording is continued for a half to one minute.

Applying descending pressure steps, the recording is started with a rise in the pressure in the eye to 15 mmHg added to P_{a}. After about half a minute it is reduced 5 mmHg and the recording is continued for about 3 minutes. Then the P_t is lowered 4 mmHg further and the recording is continued for another 3 minutes. The advantage of this technique is that the range of applanated areas used at the last two P_t levels is about the same. The main disadvantage is the sudden increase in intraocular pressure of 15 mmHg, similar to that caused by a Schiøtz tonometer.

To estimate a larger range of the volume pressure relationship than that obtained by the above methods, it is essential to use as much as possible of the available volume displaceable by applanation to increase the pressure in the eye. This can be done by performing short recordings at each P_t level to minimize outflow of the content of the eye. The P_t levels used are P_{a} + 6 mmHg and further increase in steps of 4 mmHg. To estimate changes in the intraocular volume over a longer time, recordings of applanating force at only one P_t level are used.

The apparatus is based on the following principle The applanating surface is a wall of a *pressure chamber the central aperture* of which is covered with a flexible membrane. The curvature of this membrane indicates any pressure difference between the eye and the pressure chamber An electric signal indicating the degree of curvature of the membrane controls the applanating force A small change in the pressure difference between the eye and the pressure chamber is compensated by a change in the applanating force by means of a servo system Rapid changes in intraocular pressure as normally caused by the pulse are compensated by the applanating force to probably less than half a mmHg Slower changes in the intraocular pressure are almost *completely eliminated*

The apparatus makes it possible to record continuously the applanating force and at the same time estimate the P_t The applanated area is calculated according to the Imbert Fick law The relationship between the applanated area and the volume displaced by applanation is discussed previously(15) Calculation of the displaced volume from the applanated area gives the possibility of estimating changes in intraocular volume A recording of the applanating force then makes it possible to estimate continuously changes in intraocular volume at constant P_t

A decrease in the content of aqueous humour per time unit can be expressed as a facility of aqueous outflow By using more than one P_t-level any influence of the outflow pressure on the facility of outflow can be studied

To calculate the facility of aqueous outflow the increase in outflow pressure has to be known With additional pressure increase the effects of changes in the intraocular pressure of the untouched eye and in the episcleral venous pressure *as well as an error in the P_t-determination are reduced* With this additional increase follows an increasing initial applanation whereby a smaller volume of aqueous humour displaceable by applanation is left for estimation of a decrease in the intraocular volume This has to be considered when the P_t is chosen

By using several levels of P_t the change in the displaced volume corresponding to the change in P_t can be calculated Such a procedure makes it possible to estimate the volume pressure relationship in the living eye This relationship is influenced by change in the content of the eye and change in the distention *of the ocular* coats

The pressure in the untouched eye is submitted to normal variations Repeated measurements by applanation tonometry result in a gradual lowering of the readings as reported by several authors(1 6 10 13 14) The relation between the pressure in the untouched eye and that during tonographic experiments is discussed by Goldmann(6) *In the present study the stabilized reading* after repeated measurements is accepted as the basic intraocular pressure level on which the *choice of P_t* is based

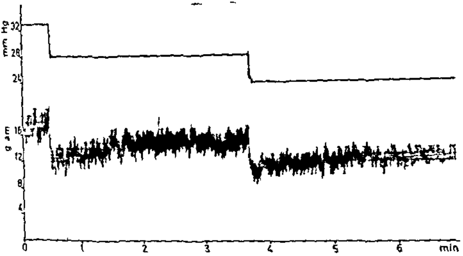


Fig 9
A recordin of applanating force with descending pressure steps otherwise equal to Fig 1

In principle different factors causing changes in the intraocular volume cannot be distinguished from each other These factors might be changes in the content of aqueous humour and of blood within the eye in distention of the ocular coats and changes due to extraocular factors However in the present

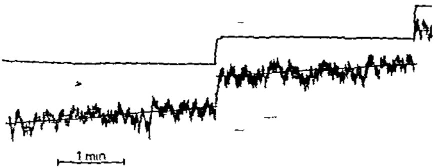


Fig 3
Example of a recording of applanating force with waves and the continuous increase in displaced volume illustrated by straight lines

Results and Discussion

Recordings of applanating force with the main techniques are shown in Fig 1 (ascending pressure steps) and in Fig 2 (descending pressure steps) The lower tracing registers the applanating force and the upper one the preset P_t The rapid oscillating of the applanating force is synchronous with and obviously induced by the pulse At every moment the applanating force corresponds within the errors of the method to the displaced volume necessary to keep the intraocular pressure at a preset and constant level The steps seen in the recordings are caused by changes in P_t which are induced by changes in the pressure in the pressure chamber The slope of the tracing of the applanating force between the steps corresponds to the continuous increase in displaced volume during the experiment

In addition to the pulse induced changes in the applanating force super imposed rythmical oscillatory changes are found These will be called waves and have different frequencies Small waves with a frequency of 10–20 cycles/minute are sometimes seen These are probably due to the breathing and will not by analysed further Large waves of still lower frequency are nearly always present in the recordings This is exemplified in Fig 3 and 4 where the waves are pronounced

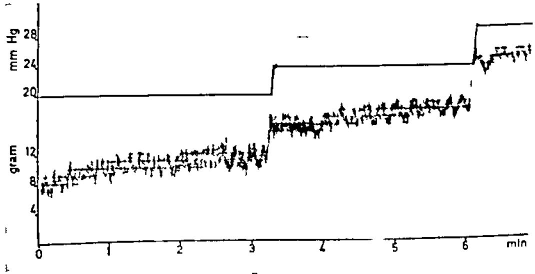


Fig 1

A recording of applanatin f e with ascending pressure ps The lower tracing shows the applanating force and the upper tracing shows the preset P_t Note the increase in the appl at ng force when the P_t i increa ed

In the analysis of the recording three main problems will be considered

1 Volume pressure relationship

2 Volume changes due to changes in blood content

3 Volume changes due to changes in aqueous humour content

1 The experiment starts by measuring the intraocular pressure as the mean of the readings i e as the mean of the pulse induced variations of the intra ocular pressure At the start of the recording of the applanating force a pulse induced change in the intraocular volume at constant intraocular pressure occurs The mean of the applanating force at the start is estimated and the displaced volume is calculated which then corresponds to the pressure increase from the P_a to the P_t At each pressure change during the experiment the simultaneous change in displaced volume is calculated in the same way The present method then gives the possibility of estimating the volume pressure relationship

2 The change in intraocular volume corresponding to a wave is calculated as follows The mean applanating force is estimated as the mean of the pulse induced amplitude The displaced volume at the peaks of the waves are cal

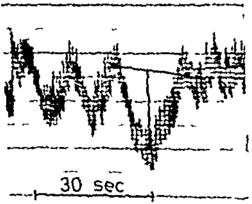


Fig 3

Diagram showing the points of the tracing from which the change in intraocular volume slower than that caused by the pulse is estimated The end points of the vertical bar are the base of the calculation

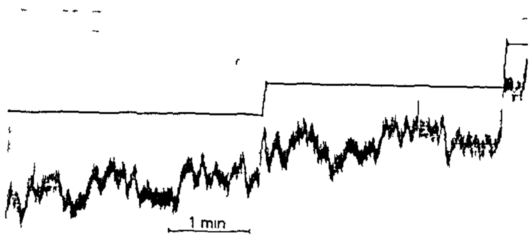


Fig 4
Example of a recording of applanating force with pronounced irregular waves and which is rejected as unsuitable for estimation of the continuous increase in displaced *volume*

study oscillatory changes of the intraocular volume (waves) are regarded as due to changes in the content of blood and a continuous steady decrease in the intraocular volume is regarded as due to a decrease in the content of the aqueous humour It must be kept in mind that during application of the present method any existing pressure sensitive mechanism in the eye for controlling its content is suppressed by keeping the intraocular pressure constant

Rapid changes in the fluid content within the eye are caused by the pulse The ocular pulse has previously been investigated in man by different methods (3 7 11 and others) These methods have been concerned with the pressure induced amplitude of the recorded pulse and have been used for studies of carotid occlusive diseases(2 3 5 12) and central vein thrombosis(4) They have also been applied to glaucomatous eyes(9) and eyes with a choroidal melanoma(8) Using recordings of applanating force at constant intraocular pressure the amplitude of the pulse induced variation of the aplanating force can be used to calculate the blood volume of each heart beat which is superimposed on the basic blood volume However the relationship between basic blood volume and pulse induced changes in volume cannot be determined As information on the pulse induced change in the blood volume alone regarded to be of limited interest this will not be considered further A stud of oscillatory changes of the intraocular volume of less frequency than pulse and respiration is however considered to be of interest

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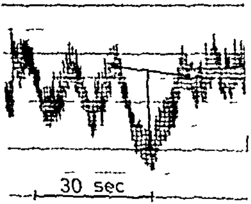


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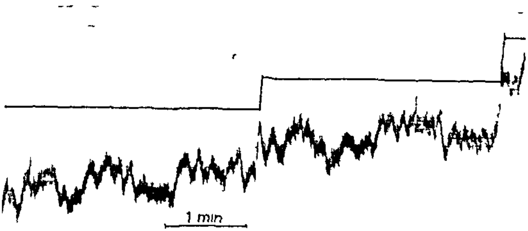


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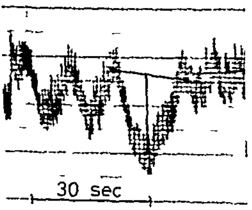


Fig 3
Diagram showing the points of the tracing from which the change in intraocular volume slower than that caused by the pulse is estimated The end points of the vertical bar are the base of the calculation

culated The intraocular volume change is then calculated as the difference in displaced volume as illustrated in Fig 5

3 To estimate a continuous steady decrease in the intraocular volume at constant intraocular pressure the slope of the applanating force between two pressure steps is estimated (the best possible straight line is drawn in the middle of the pulse induced range) as exemplified in Fig 3 The displaced volumes at the beginning and at the end of each pressure level are calculated The difference between these is then the increase in displaced volume which can be expressed in μl/min The occurrence of large slow waves sometimes makes it impossible to estimate any continuous slope of the applanating force Example of an irregular but still accepted recording is shown in Fig 3 whereas that shown in Fig 4 is rejected About one third of all investigated subjects showed such large waves that it was considered impossible to get sufficient accuracy

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THE INFLUENCE OF AGE ON PERFORMANCE IN THE PANEL D 15 COLOUR VISION TEST

BY

J HELVE and U KRAUSE

The colour vision of the better eye of 220 elderly people (mean age 74 years) was examined by using the Panel D 15 test in order to determine how often unselected elderly people fail this test and which types of defects are present Of the 16 subjects who failed the test 8 had a tritan defect one had a protan defect and one a deutan defect (both men) and 6 could not be classified Eleven persons could not perform the test and most of these had very low visual acuity Five of the 8 tritan cases had severe macular degeneration and of the 6 subjects (5 women 1 man) who could not be classified 3 also had severe macular degeneration Three subjects one a woman who had a tritan defect and one woman and one man who could not be classified had eyes that apart from the senile discoloration of the lens were otherwise normal According to the present study it seems that senile discoloration of the human lens may be the cause of failure in the Panel D 15 test

Key words Panel D 15 – age – colour vision – macular degeneration – lens

Colour vision alters with advancing age (Lakowski 1958 Verriest 1963) Verriest (1963) using the Farnsworth Munsell 100 hue test showed that hue discrimination in older age groups is especially weak in the blue green and in

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the red hues According to him factors which obviously interfere with colour discrimination in older persons are the senile yellowing of the lens the narrowing of the pupil and the frequent occurrence of some senile macular degeneration

The purpose of the present study was

- To determine the failure rate of aged subjects in the Panel D 15 test using a material collected from homes for the aged
- To determine what degree of macular degeneration causes failure in the Panel D 15 test
- To find possible reasons for failing the Panel D 15 test other than macular degeneration and congenital dyschromatopsia

Material and Methods

As a part of a mass examination 220 elderly persons from homes for the aged in Oulu were examined using the Panel D 15 test The material consisted of 123 women and 97 men The C light of the Macbeth Executive daylight illuminator was used as the light source in all examinations Only the eye with better corrected visual acuity was examined If the first pattern was too confused the test was repeated and only the retest was recorded Glasses for near correction were used in every case Mydriatics were not used during the colour vision examinations The mean age of the subjects was 74 years (range 60–90) and the mean visual acuity of the eyes was 0 6 (range 0 1–1 0) after the exclusion of 11 eyes with visual acuity less than 0 1 A routine ophthalmological examination including tonometry biomicroscopy and ophthalmoscopy was performed in every case

Results

Table I compares age and visual acuity in three groups subjects passing the Panel D 15 test subjects failing the test and subjects who could not manage the test In groups with many cases (for example normal arrangement of the caps) the mean value and range of the individual ratings are given and in groups with few cases (for example tritan) each individual value is given It can be seen from the Table that the age of those in the tritan and "unclassified groups as well as those who were unable to carry out the test did

Table I

Comparison of age and visual acuity in subjects passing the Panel D 15 test subjects failing the test and the subjects who could not perform the test

		Subjects passing the Panel D 15 test		Subjects failing the Panel D 15 test				Subjects unable to perform the test
		Normal arrangement of the caps	Disposition of adjacent caps	Protan	Deutan	Tritan	Un classified	
Women	Visual acuity	mean 0 6 range 0 1–1 0	mean 0 6 range 0 2–1 0	–	–	3 eyes <0 1 0 4 1 0	0 1 0 1 0 3 0 3 1 0	<0 1 <0 1 0 7
	Age (years)	mean 76 range 62–90	mean 78 range 67–86	–	–	61 82 84 84 87	69 78 82 86 86	76 80 86
Men	Visual acuity	mean 0 7 range 0 1–1 0	0 4 0 9 0 9 1 0	1 0	0.5	0 2 0 5 0 8	0 5	6 eyes <0 1 0 1 0 3
	Age (years)	mean 73 range 60 86	68 71 82 83	71	75	80 80 85	81	65 73 74 76 80 82 85 86
Total	Visual acuity	mean 0 6 range 0 1–1 0	mean 0 6 range 0 2–1 0	1 0	0.5	3 eyes <0 1 0 2 0 4 0 5 0 8 1 0	0 1 0 1 0 3 0 3 0 5 1 0	8 eyes <0 1 0 1 0 3 0 7
	Age (years)	mean 75 range 60–90	mean 77 range 67–86	71	75	61 80 80 82 84 84 85 87	69 78 81 82 86 86	mean 78 range 65–86
Number of subjects	Women	96	14	–	–	4	5	3
	Men	79	4	1	1	4	1	8
	Total	175	18	1	1	8	6	11

not differ greatly from the age of those passing the test On the other hand visual acuity especially in the group of subjects who could not manage the test was distinctly lower than the mean value for the subjects who passed the test

Of the 193 subjects passing the Panel D 15 test 31 had some macular de generation which was in most cases (26 out of 31) mild (visual acuity more than 0 5) and in 5 cases more severe (visual acuities 0 2 0 3 0 3 0 3 0 3) Two subjects passing the test had a certain degree of cataract (visual acuities 0 2 0 4) Two other subjects had more advanced cataract with a visual acuity of 0 1 and they still passed the Panel D 15 test Of the 193 subjects who passed the test 20 had glaucoma One glaucomatous subject with visual field defects and visual acuity of 0 1 passed the test Disposition of adjacent caps was usual (14 subjects Table I) These subjects are included among those who passed the test

Of the 290 subjects examined 16 failed the Panel D 15 test One man ar ranged the caps typically along the protan and another man typically along the deutan axis These two subjects had normal ocular fundi no cataract and normal intraocular tension The subject with the deutan defect had colour blind persons in his family In 8 cases the caps were arranged typically along the tritan axis No cases with crossings along the scotopic or tetartan axis were found Verriest (1963) states that the Panel D 15 test can provide a diagnosis even in cases with an extremely lowered visual acuity In the present study 3 subjects with a visual acuity of less than 0 1 arranged the caps typically along the tritan axis All these subjects had a marked degree of macular degenera tion A total of 5 out of the 8 subjects with tritan defect had macular degenera tion one had glaucoma (the only subject with glaucoma who failed the test) with visual field defects one had a single hypotensive aphacic eye with normal macula and one subject s eye was quite normal except for the senile discolora tion of the lens In 6 cases (5 women 1 man) the pattern in the Panel D 15 test was so confused that no diagnosis could be made Three of these cases had macular degeneration one had such an extensive cataract that the macular area could not be examined and two subjects (both women) had apparently normal eyes (visual acuities 0 8 and 1 0) except for the brownish discoloration of the lens Some subjects (11 cases) could not arrange the caps at all In most of these cases low visual acuity seemed to be the reason In 8 of these eyes the visual acuity was less than 0 1 one had a visual acuity of 0 1 and one of 0 3 In one case a subject with normal visual acuity was obviously deficient in intelligence

Discussion

The purpose of the Panel D 15 test is to differentiate between severely and slightly colour defective persons (Farnsworth 1947) This explains the fact that 31 eyes with macular degeneration passed the test in the present study If visual acuity is too low the test cannot be performed and for this particular reason at least 8 persons in the present study could not carry out the test Of the 209 subjects (eyes) capable of taking the test, 16 (7 7 per cent) failed to pass it The reason for failure was mostly a macular degeneration which in these cases was more serious (when ophthalmoscopy and visual acuity were used as criteria) than in the 31 cases of macular degeneration which passed the test One glaucomatous but otherwise normal subject made a tritan pattern On the other hand 20 cases with glaucoma passed the test According to the present study it seems that when old people are the subjects of examination the pattern is often so confused (in the present study in 6 out of the 16 eyes which failed the test) that no diagnosis of the type of colour vision defect can be made Interestingly in 3 cases the senile discoloration of the lens seemed to be the only reason for failing the Panel D 15 test

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Sorsby Arnold (ed) Modern Ophthalmology 2nd edition. Four volumes Butterworth London 1972

Volume I (ISBN 0 407 06042 1) Basic Aspects 609 pages Price purchased separately £ 13 Volume 2 (ISBN 0 407 06043 X) Systemic Aspects 746 pages Price purchased separately £ 16 Volume 3 (ISBN 0 407 06044 8) and volume 4 (ISBN 0 407 06045 6) Topical Aspects 1 41 pages together Volume 3 & 4 are sold together price £ 31 Four volume set (ISBN 0 407 06041 3) price £ 56 + postage

The first edition of Modern Ophthalmology appeared in 1963/64 and has in our area and elsewhere been considered a most valuable textbook of ophthalmology In troduction to a speciality must be obtained by studying a suitable short presentation Every ophthalmologist to be very soon feels the need for a comprehensive and didactic textbook to become his friend and adviser through his years of education and in his later professional activity In this respect the four volumes of *Modern Ophthalmology* surely represent a wise choice

Eighty one experts in ophthalmology from Great Britain the United States and Canada have contributed to the second and up to-date revised edition. The basic structure of *Modern Ophthalmology* still emphasises aetiology as far as it goes The work s popularity is well deserved

P Brændstrup

Conley *John* & *Dickinson John T* (ed) Plastic and Reconstructive Surgery of the Face and Neck Vols 1 and 2 Georg Thieme Stuttgart 1972 252 + 368 pages 368 + 605 illustrations Price DM 79 + 118

This is a selection of papers from the First International Symposium on Plastic and Reconstructive Surgery of the Face and Neck held in New York in 1970 and attended by general plastic surgeons maxillo facial surgeons oral surgeons cosmetic surgeons prosthodontists and otologic and ophthalmic surgeons

The first volume covers aesthetic surgery the second rehabilitative surgery

Of special interest for ophthalmic surgeons are chapters concerning blepharoplasty *treatment* of fat pads in the region of the eyelids tatooing of naevus flammeus with high speed injection machine silicone injections in lipodystrophy *treatment of* chemical burns with grafts and primary scalp flap reconstruction to cover the maxillo orbital region after extended maxillectomy and orbitectomy instead of prosthesis

Several papers cover ptose operations (external and internal approach brow suspension – and the indications for these different methods) entropion operations (eyelid sutures without skin excision in acute entropion several methods in chronic entropion buccal mucous membrane graft) and orbital implant

Interesting papers deal with face lift operations (temple lift brow lift) dermabrasia chemosurgery hair transplantation free graft regional flaps etc.

This book represents a gigantic source of material from many disciplines with some interest for the ophthalmic surgeon.

M S Norn

Discussion

The purpose of the Panel D 15 test is to differentiate between severely and slightly colour defective persons (Farnsworth 1947) This explains the fact that 31 eyes with macular degeneration passed the test in the present study If visual acuity is too low the test cannot be performed and for this particular reason at least 8 persons in the present study could not carry out the test Of the 209 subjects (eyes) capable of taking the test 16 (7 7 per cent) failed to pass it The reason for failure was mostly a macular degeneration which in these cases was more serious (when ophthalmoscopy and visual acuity were used as criteria) than in the 31 cases of macular degeneration which passed the test One glaucomatous but otherwise normal subject made a tritan pattern On the other hand 20 cases with glaucoma passed the test According to the present study it seems that when old people are the subjects of examination the pattern is often so confused (in the present study in 6 out of the 16 eyes which failed the test) that no diagnosis of the type of colour vision defect can be made Interestingly in 3 cases the senile discoloration of the lens seemed to be the only reason for failing the Panel D 15 test

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Hartstein Jack Review of Refraction The C V Mosby Company St Louis 1971 ?46 pages 100 illustrations Price $ 9 75

The author is Assistant Professor of clinical ophthalmology and a Lecturer in refrac tion in St Louis Mo The book offers residents in ophthalmology a text written as questions and answers (e g Define phoria? What is a cross cylinder?) a form that often appears forced because it does not always apply to the topic. The book contains 21 chapters completely covering the subject and to some degree overlapping neigh bouring fields – thus e g 7 pages are expended on description of basic ophthalmo scopic technique and ?? pages on strabismus Dynamic retinoscopy is expanded to 7 pages keratometry to 11 pages Contact lenses are only briefly mentioned As basic clinical refractive procedure the author favours fogging with plus lenses followed by determination of astigmatism with clock dial and cylinder glasses and terminated by adding minus spheres to best visual acuity The author reckons L T U V and C as the hardest letters to read on the Snellen chart this is in direct opposition to the experiences of most ophthalmologists References consist of a booklist of 17 items whereas the index is complete The book can be recommended for younger ophthalmo logists with energy for self examination

Ole I Nissen

Rasskoff Sava Die diabetische Retinopathie und ihre Behandlung mit Lichtkoagula tion (Diabetic Retinopathy and Its Treatment with Photocoagulation) 33? pages 130 photographs and figures Dr W Junk N V Publishers The Hague 1972 Price Hfl 100

This is a thesis from the University Eye Clinic of Rotterdam

The first 134 pages give an elaborate description of diabetic retinopathy including morphology histology course prognosis and classification

Destruction of the existing retinal vasculature stimulates neovascularisation The structural formation of the new vessels is determined by the interrelationship of the bloodflow inside the capillaries and the tissue resistance outside the vessels leading the new vessels to the surface of the retina In this place they are not only useless but also harmful since the blood is lead away from the still functioning capillaries Destruction of newly formed vessels becomes the rationale of photocoagulation

A total of 177 patients were treated with Xenon arc photocoagulation Average follow up time was more than 1 5 years 196 eyes were treated once 47 eyes more than once In 5? patients in whom both eyes were approximately equally affected one eye was treated and the other served as control Often 250 or 300 or more coagulations were given per session without ill effects

The majority of the cases consisted of advanced retinopathies since early retino pathy has the possibility of spontaneous improvement and in advanced endstages there is no indication for treatment

After photocoagulation 123 eyes had improved 65 were unchanged and 55 were impaired In the control group of 5 patients improvement of the treated eye was generally observed

This study is favourably placed in the expanding literature of photocoagulation of diabetic retinopathy

P Brændstrup

Rubin Melvin R Optics for Clinicians TRIAD Scientific Publishers P O Box 13096 University Station Gainesville Florida 32601 U S A

The older generation of ophthalmologists in Europe had a *rather long and penetrating* education in physiological optics The textbook of Helmholtz was an essential part of their studies The new generation of ophthalmologists tend to ignore optics and the knowledge they obtain on this subject in school does not provide a satisfactory background for an understanding of most of the basic optical literature

Optics for Clinicians by Melvin L Rubin is a book with a new approach to the subject To a certain degree based upon Dr Paul Boeder's lectures in the Lancaster course this book is a simple yet adequate introduction to optics Using the vergence conception and with a minimum of mathematics the author tries to give the reader a maximum of understanding By its rather personal style the author makes optics thrilling which is essential if the young resident is to overcome his inborn dislike for the subject

After the first part that deals with basic optics the author goes in to the more classical visual optics Not only the practice of refraction but also the correction of certain states of errors and aberrations are discussed The last part deals with the *optics of certain instruments*

The whole book is illustrated with well chosen simple figures which make it easy to understand the text but which also are excellent in teaching In the preface the author stresses the fact that the book is a *teaching manual to be read straight through* To this one could add that it is easy to read that one reads it with pleasure and that it can be highly recommended to teachers of visual optics as well as to residents in ophthalmology

Bjorn Tengroth

Fine Ben S & Yanoff Myron Ocular Histology A Text and Atlas 260 pages 490 illustrations 19 in full color Harper & Row New York 1972 Price $ 25

From the Registry of Ophthalmic Pathology of the Armed Forces Institute of Pathology Washington D C – a renown mecca of ophthalmology – has emanated this work on the histology and cytology of the eye The authors both of whom are eye specialists in addition to being ophthalmopathologists obviously have had eye specialists in mind in their presentation of the subject matter The work is introduced by chapters on electronmicroscopic technique and interpretation as well as the structure of the cells and tissue after which there follows a detailed analysis of all the tissues of the eye Emphasis is placed on electronmicroscopic photographs (including scanning electron microscopy) To clarify the ground connection with light microscopy and biomicroscopy which certainly can be difficult for ophthalmologists illustrations with light microscopic photos and schematic drawings are given Clinical observations of normal and diseased conditions in the eye frequently are correlated

The illustrated material is considerable and inclusive and the authors great expertise and critical sense leave their mark on this book which can be recommended to all who wish a short up to date survey of the subject

S Ry Andersen

AUTHORS INDEX

Veirs Everett R Ärztlicher Rat bei grünem Star Ursachen Folgen Behandlung des Glaukoms Georg Thieme Stuttgart 1972 VIII 56 pages 14 illustrations

The fact that there is now a German translation of the author's original *So You Have Glaucoma* must be an expression of the common tendency to spread what information is available about a series of chronic diseases A thorough description is given of *anatomy physiology and symptomatology* as well as treatment for the various forms of glaucoma – buphthalmia open angle glaucoma angle closure glaucoma and secondary glaucoma The book accomplishes its purpose of answering in a well balanced manner a list of typical questions patients ask There is however one drawback in that the author has chosen to include in the one book all types of glaucoma and thereby gives more comprehensive information than is necessary for the individual patient especially as regards the most frequently occurring glaucoma simplex

K Norskov

Deutman A F The hereditary dystrophies of the posterior pole of the eye Royal Vangorcum Ltd Assen The Netherlands 1971 484 pages Price Hfl 146–

This is not only a beautiful thesis but an excellent textbook of the hereditary dystrophies of the central retina and choroid

The confusion in the classification and differential diagnosis of hereditary dystrophies of the posterior pole has always been great and even if the author has not been able to solve all classification problems he has succeeded in solving most For the author – as for the reader – *there is no doubt that there are several hereditary central dystrophies* determined by several different genes but on the other hand there is great variability in the expressivity of the various genes

The results are based on a comprehensive study of 240 patients and their relatives combined with genealogical research and an exhaustive survey of the literature In all cases the usual routine examinations were made but moreover retinal function tests as ERG EOG and fluorescein angiography were carried out

In 13 chapters the different dystrophies are described and the characteristics of each affection are presented accompanied with fine photographs Interesting results have been obtained by using orthochromatic and panchromatic graphic films

The book is highly recommended and should be made available in every ophthalmological library

E Goldschmidt

AUTHORS INDEX

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SUPPLEMENTA